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PATENT DUCTUS ARTERIOSUS AND ITS SURGICAL TREATMENT *

BY

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The remarkable success that has attended surgical ligation of the patent ductus arteriosus has aroused a new interest in a unique structure and has been the means of revealing striking gaps in our knowledge of a comparatively common form of congenital heart disease. Unexpectedly, ligation of the infected ductus has shed a new light on the most serious of all forms of heart disease—bacterial endocarditis. Of vital importance in intra-uterine life, during which its purpose is to enable venous blood entering the heart from the superior vena cava to pass directly to the descending aorta and thence to the placenta without traversing the lungs (Barcroft, 1939), the arterial duct persisting after birth forms an arterio-venous fistula. Blood then flows continuously in large quantities from the aorta to the pulmonary artery. Hence the patent ductus throws an added burden upon the heart and upon the pulmonary and to some extent the peripheral circulations.

Problems of the Patent Ductus

Despite the enormous literature that has accumulated on this branch of congenital heart disease, we have not yet adequate solutions for many of the most fundamental of its problems. Theories and suggestions to account for the closure of the ductus are many, but the factors determining the natural process of occlusion, or permitting the persistence of the channel for months or years or throughout life, are mysteries for which so far we have no entirely satisfactory explanations. Wells (1908) and Abbot (1927) have summarized the more important suggestions advanced to account for the mechanism of closure, none of which in the light of present day knowledge can be regarded as adequate without experimental proof. Expansion of the bronchi compressing the ductus, inflation of the lungs with consequent readjustment of the thoracic viscera leading to stretching and obliteration of the ductus, local thrombosis within the duct as a result of changes in blood pressure in the two circuits, the occlusive effect of a valve-like fold of aortic endothelium overlying the orifice of the channel, the constrictive effect of the recurrent laryngeal nerve as the viscera sink lower in the thorax, are among the possibilities which in the past have been advanced and seriously considered by various authors. Kennedy and Clark (1942) and Kennedy (1942) have demonstrated that during late fœtal life the ductus arteriosus is an active structure, responsive to certain stimuli of which at least one favouring its prompt closure is, they believe, a rich oxygen supply either by inhalation or intravenously. By the injection of radio-opaque dye into the blood stream of fœtal lambs delivered by Caesarean section, Barcroft and his collaborators (1938, 1939, 1941) have clearly demonstrated abrupt changes in the patency of the ductus so that functionally there is a rapid obliteration of its lumen even within five minutes of birth. Anatomical obliteration is a gradual process. The factors initiating the functional or primary closure, maintaining the muscular contraction of the ductal walls, and regulating the sequence of events leading to the final obliterative process, are unknown.

Similarly there has been in the past no unanimity of opinion regarding the histological structure of the ductus arteriosus, either as found in the newborn infant or in regard to the anatomical changes leading step by step to its replacement by the ligamentum arteriosum. It is natural to correlate

* The George Alexander Gibson Lecture delivered before the Royal College of Physicians of Edinburgh on October 26, 1944.

function with structure, the primary occlusion being doubtless attributable to twisting and contraction of the mass of muscle (Warren, 1886), arranged according to von Heyek (1935) in spiral form, which predominates in the ductal walls. Boyd (1941) has demonstrated a sensory innervation of the mammalian ductus, very similar to that possessed by the aorta and carotid sinus, derived from the left vagus nerve and also fine nerve fibres, presumably motor in type. The exact source of the latter is difficult to determine, but experiments suggest their parasympathetic origin (Barcroft, 1938).

The most recent and informative studies in the obliterative process have been made by Jager and Wollenman (1942). who have confirmed and extended the observations of Swensson (1939). The interior of the degenerating ductus is thrown into mounds, composed of scattered elastic fibres and masses of smooth muscle, which project into the lumen, increase in size and perhaps also in number, and lead ultimately to obliteration of the channel by their progressive replacement with collagen and eventually by firm fibrous tissue, the whole process of anatomical obliteration extending over several months. Alvarenga (1876) did not find a single example of perfect occlusion amongst 54 cases examined up to the age of four weeks. Christie (1930) found 65 per cent patent at the end of two weeks and 1 per cent at the end of the first year. The time of final closure therefore varies widely and no doubt accounts for the variations in histological description.

An adequate explanation for the persistence of the fœtal state of the ductus is even more obscure. The occasional observation of its occurrence in more than one member of the same family suggests an inherent abnormality of the germ plasm. Smith (1929) has noted its presence in twins, and Jewesbury (1912), Ellis (1933), and Brown (1939) have discovered it in sisters. De la Camp (1903) observed a series of six brothers and sisters all with the characteristic physical signs of patent ductus arteriosus. The opportunity has been taken to examine a large number of the brothers and sisters and mothers of the children in the present series without finding another example of the condition. On the other hand, reference may here be made to Case 16, a married woman with well marked signs of patent ductus arteriosus whose mother suffered from congenital heart disease (auricular septal defect) and whose first child died from congenital heart disease. The occurrence of a congenital flaw, though each of a different type, in three generations lends support to the suggestion of an hereditary defect in the germ cell. Its common association with other congenital flaws, such as coarctation of the aorta, or the valvular atresias, or in conjunction with pulmonary atelectasis, makes it possible that a raised arterial pressure may be the factor responsible for the failure of the duct to close under such circumstances.

The gaps in our knowledge of this important congenital flaw are not confined to the basic sciences. Although 45 years have elapsed since Gibson (1898) put the diagnosis of patent ductus arteriosus on a sure foundation, it is regrettable that to this day prognosis is still largely open to conjecture. The available accounts provide insufficient information to form an accurate assessment of the natural course of the disease. The frequency of the more common complications and the rate of physical deterioration are aspects of great importance to the physician faced with the problem of estimating even on the most rough and ready basis the expectation of life for his patient. Unfortunately, the considerable literature being largely pathological, composed mostly of isolated case records and therefore weighted with the unique and exceptional, tends to distort the picture as a whole. So also the limited experience of any one observer handicaps a just assessment of the fundamental clinical problem of the influence of the untreated patent ductus arteriosus on the life span of the particular patient. Bullock *et al.* (1939), reviewing eighty fatal collected cases, found that 14 per cent had died by the age of 14, 50 per cent by 30, and 71 per cent by 40. Two patients reached the age of 66 years. Similar studies led Keys and Shapiro (1943) to conclude that for those surviving to 17 patent ductus arteriosus reduced the expectation of life by about 25 years—that is, by about half. These valuable and instructive analyses are open to the criticism that the entire data have been obtained from fatal cases reported at random, which it may be argued are not strictly representative of the hazards to which living patients are exposed in that the number of survivors is unknown. Wilson and Lubschez (1942) believe that in children the surgical risks associated with ligation of the ductus far exceed the natural risk, but they admit that their series of 38 patients, considered to have uncomplicated patent ductus arteriosus, is too small to warrant absolute statements. Patent ductus arteriosus is uncommon in middle or later life and hence as a compromise it may be suggested that on the

average the statistics of Wilson and Lubschez are probably too optimistic, just as the purely pathological data perhaps over-emphasize the gravity of the risk. Larger series of patients followed over longer periods of time ought to provide the data on which more accurate figures for life expectancy may be based. Until this has been done the problem of prognosis in untreated patent ductus arteriosus will remain unsolved.

It is in the hope of providing a better understanding of some of these problems, particularly in regard to the natural course of the disease process, that the present studies were started. Prognosis is always the immediate concern of the physician, but never more so than when faced with a revolutionary form of treatment. An experience of the untreated to balance against the results obtained by the new procedure is essential in forming a judgment, after which the method can be recommended or rejected with confidence. Preliminary findings are reported in the present paper.

Diagnosis

Symptoms. Little help is to be had from a consideration of symptoms or from the build or appearance of the patient. It is more the exception than the rule to be faced with the slim, slightly built, underdeveloped, anæmic child, of a wax-like pallor and anxious countenance. To most mothers the intimation that a flaw exists in the child's heart comes as a surprise, but closer attention to the habits and reactions of the child, particularly the comparison of its behaviour with that of other members of the family at a similar age, usually leads the parents to admit, by the time age 8 or 10 is reached, that some impairment in circulatory efficiency is present. A sense of fatigue, a minor amount of breathlessness, and as the child grows older a retardation of physical development, particularly in weight and muscular development, are all features that commonly and almost imperceptibly make their appearance. Ductal patency has no specific or characteristic symptom, but the statement that it usually persists throughout childhood as a symptomless lesion is contrary to my experience. The truth of this is illustrated by the occasional observation of the mother that only after surgical ligation did she realize that previously the child had been unusually breathless. Similarly, young adults may deny any unusual degree of dyspnœa because they have become so habituated to it throughout their life as to be unaware of it. Occasionally attacks of epistaxis occur. An unusual sensitivity to cold is sometimes noted in children. Epileptiform convulsions have been described (Leech, 1932). Hoarseness from implication of the left recurrent laryngeal nerve as it rounds the aorta in the angle between the ductus and the isthmus has been recorded (Schrotter, 1901; Tileston, 1910), but is exceedingly rare. Laryngeal involvement was not observed in this series, except as a complication after operation in two patients. Cyanosis is unusual and clubbing of the fingers has not been observed. As compared with standard tables the physical development of the 13 children observed in the first decade was: above average 2, average 7, and under average 4; this agrees with the finding of Muir and Brown who noted only 5 of 20 patients to be below the standard development.

The Auscultatory Signs. The peculiar and characteristic murmur originally emphasized and described by Gibson (1898, 1900, 1906) is of the first importance in diagnosis. The murmur, systolo-diastolic in time and best heard to the left of the upper sternum, has been described as humming, purring, tearing, churning, sawing, machinery-like, the "train-in-a-tunnel" sound, or as rolls of thunder. The essential feature emphasized by Gibson (1906) in his original description is its continuous quality.

> "It begins," he says, "after the commencement of the first sound. It is continued during the latter part of that sound and the whole of the short pause. It persists through the second sound and dies away gradually during the long pause. The murmur is distinctly rough and thrilling. It begins softly and increases in intensity so as to reach its acme just about or immediately after the incidence of the second sound and from that point gradually wanes till its termination. The second can be heard to be loud and clanging."

Gibson drew attention to the rhythm of the thrill and murmur diagrammatically in his book (1898) and again in 1900. However debatable the justification for attaching to physical signs the name of the original observer, the custom persists and not least in the auscultatory phenomena of organic heart disease. I suggest that the pathognomonic murmur, to which

in recent years so many descriptions have been applied, be henceforth known as the Gibson murmur. For clinical purposes it can then be described as loud (" rolling thunder "), moderate (" churning " or " machinery ") or faint (" humming-top ").

As a rule in children the murmur is found maximum in the region of the second left intercostal space close to the sternum, but sometimes just below the sternal end of the left clavicle. Depending on its intensity, so may it be heard over a wide area, but usually the continuous quality is localized to a strictly limited area. It can often be heard at the back in the left interscapular region or above the spine of the scapula. On occasions it is maximum to the left of the third or fourth thoracic spine, at least in its systolic accentuation, which then suggests the presence of an associated coarctation of the aorta. As the child approaches adult life, with dilatation and elevation of the pulmonary artery and its branches within the mediastinum, the murmur commonly grows louder. The site of maximum intensity depends on the proximity of the pulmonary artery to the chest wall, and the degree and direction of the artery's dilatation. This is a gradual process. Commonly the pulmonary artery enlarges more and more to the left with the result that the murmur can then be heard over a wider area, and of greater importance from a diagnostic point of view, its maximum intensity is then often found more and more to the left of the mid-line. So much is this the case that the murmur, though loud, is located so far to the left as to be overlooked. The greatest dilatation of the pulmonary artery is commonly found when subacute bacterial endarteritis involves the vessel wall. The site of the characteristic murmur of the patent ductus may then be removed a full hand's breadth from the sternum in the second or third left interspace. Auscultation over the usual area (second space close to the sternal border) may reveal healthy sounds or no more than a long systolic murmur and an average or accentuated second sound. As the pulmonary artery enlarges the murmur must be sought farther afield.

Even in adults the continuous murmur of the patent ductus can occasionally prove exceedingly elusive. It may be so faint as to be almost inaudible and of a pitch and intensity not far removed from the breath sounds. With the patient semi-recumbent, and with breathing checked at the end of expiration, preferably just after a few full deep breaths which accentuate the murmur by increasing blood flow through the lungs, the distant hum of the Gibson murmur may then be more readily detected, though limited perhaps to an area no bigger than the bell of the stethoscope. Other auscultatory signs may accompany and overshadow the Gibson murmur and by their very intensity confuse the diagnosis. A systolic murmur is often widely heard over the præcordium, usually maximum towards the base, and accompanying it along the left sternal border; a diastolic may also occasionally be detected. These systolic and diastolic murmurs are all too apt to mislead. Neither is necessarily a result of a valvular endocarditis to which they may be attributed, particularly if insufficient care fails to reveal the latent Gibson hum and dilatation of the pulmonary artery. Laubry and Pezzi (1921) attribute the diastolic murmur to the pulmonary incompetence, the result of high pressure in the pulmonary artery, but the pulmonary arteries showing the maximum dilatation (e.g. Case 14) do not necessarily produce this phenomenon. With a rheumatic history the diastolic murmur suggests aortic incompetence, and with septicæmic signs a bacterial endocarditis. The pulmonary second sound is almost invariably accentuated or reduplicated—a fact of some importance in excluding other congenital flaws of the pulmonary artery. The intensity of the second sound should be studied immediately below the point of maximum intensity of the murmur.

The character of the murmur varies with the age of the patient. At birth and in infancy physical signs may be wanting. At two or three years routine examination may show a basal systolic murmur, more to the left side and radiating out below the clavicle without the intensity to suggest its organic origin. By the third or fourth year the murmur has usually developed something of a continuous quality, with systolic accentuation and maximum intensity in the pulmonary area. Signs develop with varying rapidity in different children.

In Case 2 at the age of 4 they were fully developed (a loud Gibson murmur and thrill, and the heart enlarged), whereas in Case 17 the continuous humming quality was not detected until the age of 7, when the child had been under observation for two years with a pulmonary systolic murmur and accentuated pulmonary second sound with dilatation of the pulmonary artery. Other examples could be quoted. As a rule the diagnosis can be made with confidence from the auscultatory signs alone by the fourth or fifth year. As age progresses the signs generally become more obvious, the murmur coarser and harsher, or they may remain stationary. Rarely they may regress or disappear entirely and leave no trace.

Radiological Examination. Radiology provides evidence of the state of the pulmonary artery and its branches. Enlargement of the pulmonary artery is usually evident in the frontal view (Fig. 1). It extends to the left as a semi-circular shadow lying between the aortic knuckle above and the ventricular mass below. One of the earliest radiological findings to be described in the examination of the heart, the bulging middle arc on the left cardiac border, has been called the X-ray cap of Zinn (1898). In the present series evidence of pulmonary dilatation was only lacking in 3 (Cases 2, 21, and 25, Fig. 2) of the 27 examined radiologically.

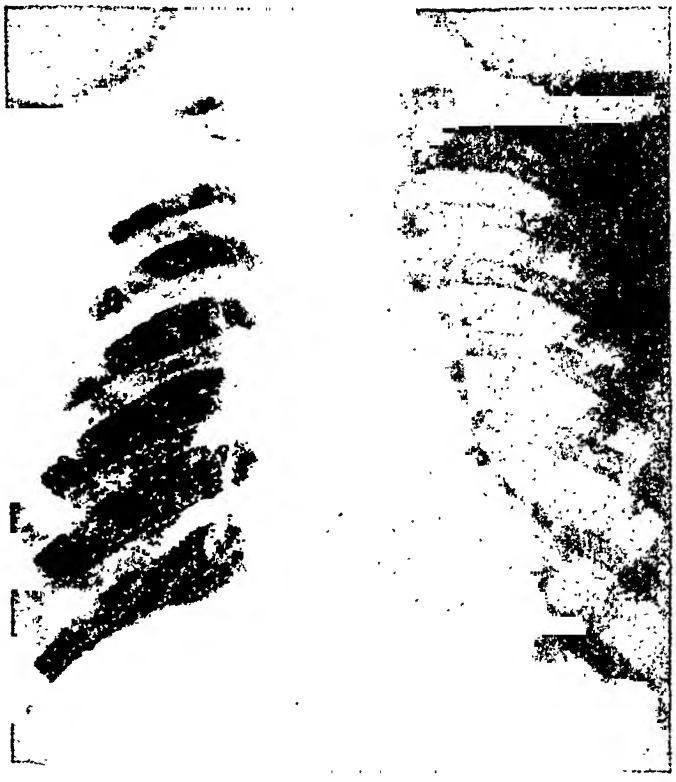

FIG. 1.—Teleradiogram. Characteristic heart outline of patent ductus arteriosus (*P.D.A.*) in a youth, aged 18 (Case 9). The heart size is within normal limits but the pulmonary arc makes a prominent bulge below the aortic knob. There is increased vascularity of the lung fields.

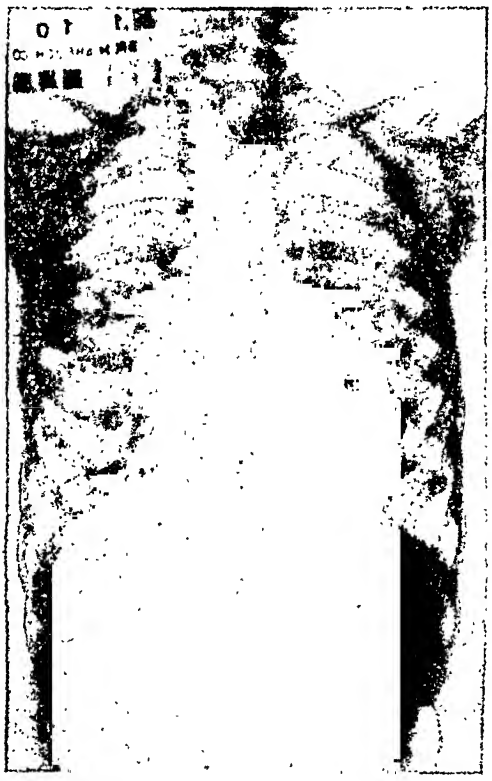

FIG. 2.—Teleradiogram. An enlarged heart in a child, aged 4, with greatly increased vascularity of the lungs, and prominent branches of the pulmonary artery, but the pulmonary arc is *not* prominent. *P.D.A.* confirmed at operation (Case 2).

In the right oblique position the trunk of the vessel can often be rendered prominent as a bulge over the upper third of the ventricular shadow. Screen examination should never be omitted. It provides visual evidence of the size of the pulmonary artery, the range of its expansion, the state of the various chambers of the heart, particularly the left ventricle, and the extent of the systolic excursion: the latter, taken with the degree of pulsation in the pulmonary artery, is almost always increased and provides useful confirmation of the nature of the defect. There are other radiological signs: dilatation of the right and left pulmonary artery branches, congestion of the lung fields as shown by a diffuse mottling radiating out

from the hila towards the periphery, the " hilar dance ", a systolic expansion in the arteries of the lung root, and dilatation of the left auricle, the two latter being the least common in my experience—a view contrary to that expressed by Donovan, Neuhauser, and Sosman (1943), but supported by Steinberg (1943).

The size of the heart was determined according to the four grades employed clinically, and the cases studied may accordingly be grouped as follows:

(A) no enlargement—7 patients (Cases 9, 16, 19, 24, 26, 27, 28);
(B) enlarged to mid-clavicular line—15 patients (Cases 2, 4, 5, 6, 7, 8, 10, 11, 12, 13, 17, 18, 21, 22, 25);
(C) enlarged to within anterior axillary line—2 patients (Cases 3 and 20);
(D) enlarged beyond anterior axillary line—1 patient (Case 15);
(E) enlarged to mid-axillary line—3 patients (Cases 1, 14, 23).

Gross enlargement of the heart is therefore uncommon in uncomplicated patency of the ductus. This agrees with the opinion expressed by Roesler (1936) and others. When striking cardiac enlargement does exist it suggests complicating factors, either some other associated congenital flaw, or an infected ductus and pulmonary artery (Cases 1, 14, and 23).

Blood Pressure. Few studies have been reported on the blood pressure findings in this congenital flaw, perhaps for the reason that its diagnostic value has only recently been emphasized (Bohn, 1938). Readings have been recorded repeatedly in all the patients of the present series with the exception of one (Case 23). Blood pressure studies on healthy children are not numerous and it is often difficult to obtain reliable readings, the end point for diastolic pressure commonly lacking definition in the child. By the usual technique the sounds over the artery, brachial or popliteal, may be inaudible in the infant.

It is common to find amongst young children that the standard cuff as used in the adult is of too large a size, the edges overlapping the cubital fossa below and the shoulder above. Figures obtained under such circumstances tend to be too low, just as they tend to be too high when the standard cuff is too small a fit for the obese arm of an overweight woman. In the child, when the standard cuff appears too large for the arm, my custom is to fold it lengthwise, thereby reducing the width of the bag by half, before applying the cuff to the arm. This is a satisfactory method, yielding more accurate figures, comparable with those in the adult. According to Judson and Nicholson (1914) the diastolic pressure in healthy children between the ages of 3 and 15 ranges between 64 and 71; and the systolic between 91 and 106. On the average a healthy child under the age of 10 has blood pressure figures in the neighbourhood of 98/68 with a pulse pressure of 30.

Table I shows the average blood pressure for each ten-year period, minimum readings being selected for each individual. In the first decade (13 patients) the pulse pressure, as compared with healthy children of the same age, is increased as a result of a fall in the diastolic level. The numbers in the later age groups are small, but if we average the remaining 15

TABLE I

AVERAGE MINIMAL BLOOD-PRESSURE IN AGE GROUPS

Age period	No. in group	Average blood pressure readings		
		Systolic P.	Diastolic P.	Pulse P.
0–10	13	95	48	47
11–20	8	115	52	63
21–30	4	128	43	85
31–40	2	136	66	70
41–50	1	168	88	80
11–50	15	125	53	72

observations extending over the age period 11–50 it is found that the diastolic pressure is but little altered with age, being 53 mm. The increase in pulse pressure (72 mm. for this older group) is attributable to a rise in the average of the systolic pressures (125 mm.). It would therefore appear that in those surviving childhood the diastolic pressure keeps fairly constant.

The level of diastolic pressure may be correlated with the size of the shunt, a ductus of larger bore being associated with a lower diastolic reading; thus the pulse pressure is a rough measure of the burden thrown on the left ventricle.

Many other factors influence the level of diastolic pressure; the peripheral resistance in the pulmonary and peripheral circuits, the elasticity of the greater vessels, the pulse rate, bodily posture, phase of respiration, metabolic state, and emotional tension, must all play a part. In the absence of satisfactory help from angiocardiography (Stewart, 1941; Steinberg, 1943) the magnitude of the leak from the peripheral circuit and the size of the ductus are probably best estimated for clinical purposes by noting the degree of the pulmonary artery dilatation, the vascularity of the lungs, and the intensity of the murmur, which presumably is influenced greatly by pressure changes within the pulmonary artery and the turbulence excited by whirling blood currents. By excluding or minimizing the influence of various extraneous factors, blood pressure readings in the basal state or during sleep may provide a rough clue to the size of the ductus, but without these precautions blood pressure readings in themselves have not been found helpful in gauging the bore of the channel. Employing simultaneous rœntgen-kymograms with acetylene rebreathing experiments, Keys and Friedell (1939) have found it possible to estimate the flow through the ductus by determinations of the right and left ventricular outputs; the method is complicated but instructive.

The Exercise Test. Bohn (1938) has pointed out the value of a simple exercise test in diagnosis. After noting the resting pressures, both of which may be perfectly normal, further readings are recorded immediately after a simple exercise test, even ten " knee-bends " being sufficient. The blood pressure must be recorded repeatedly, more than once if possible within the first minute. The systolic pressure and pulse rate may rise but the characteristic feature is the transient drop in diastolic pressure, often nearly to zero, and its prompt recovery within a minute or two. The enormous but temporary increase in the amplitude of the pulse is accompanied by tachycardia, bounding neck vessels, the Corrigan phenomenon, and capillary pulsation. Presumably under the influence of physical activity an increased shunt of blood from the aorta to the pulmonary circuit occurs as a result of vascular dilatation through the lungs. Secondly, a dilatation of the peripheral vessels, to facilitate an adequate blood supply to the active muscles, no doubt exaggerates the circulatory defect. From experience of this test, it is necessary to emphasize that the exercise must be done briskly, and to facilitate as many readings as possible within the critical first minute of completion of the muscular activity, the blood pressure cuff must be applied beforehand and worn throughout the test. Fig. 3 shows the type of reaction obtained in Case 27 : under resting conditions this man had normal blood pressure readings ; exercise induces an abrupt fall to 20 mm. in diastolic pressure.

Blood pressure readings after exercise are of particular value in diagnosis when the typical Gibson murmur is absent. Bohn (1938) believes that this can be the most important objective evidence in diagnosis. Thus in a young person a basal systolic murmur with an over-active heart and accentuation of the second pulmonary sound should not be lightly dismissed without a simple exercise test. Similarly, a raised pulse pressure in a child, lying comfortable at rest, afebrile, and without local evidence of aortic regurgitation, is very suggestive of a patent ductus arteriosus.

Peripheral Signs. There are other physical signs to be detected occasionally in the peripheral circulation. In themselves they are seldom, if ever, of help in diagnosis as their presence depends largely on a major defect itself accompanied by gross local signs readily detectable. Advanced cases, even at rest, may show most of the circulatory phenomena so commonly associated with a leaking aortic valve: facial pallor, bounding neck vessels, and the Corrigan pulse. In such instances the

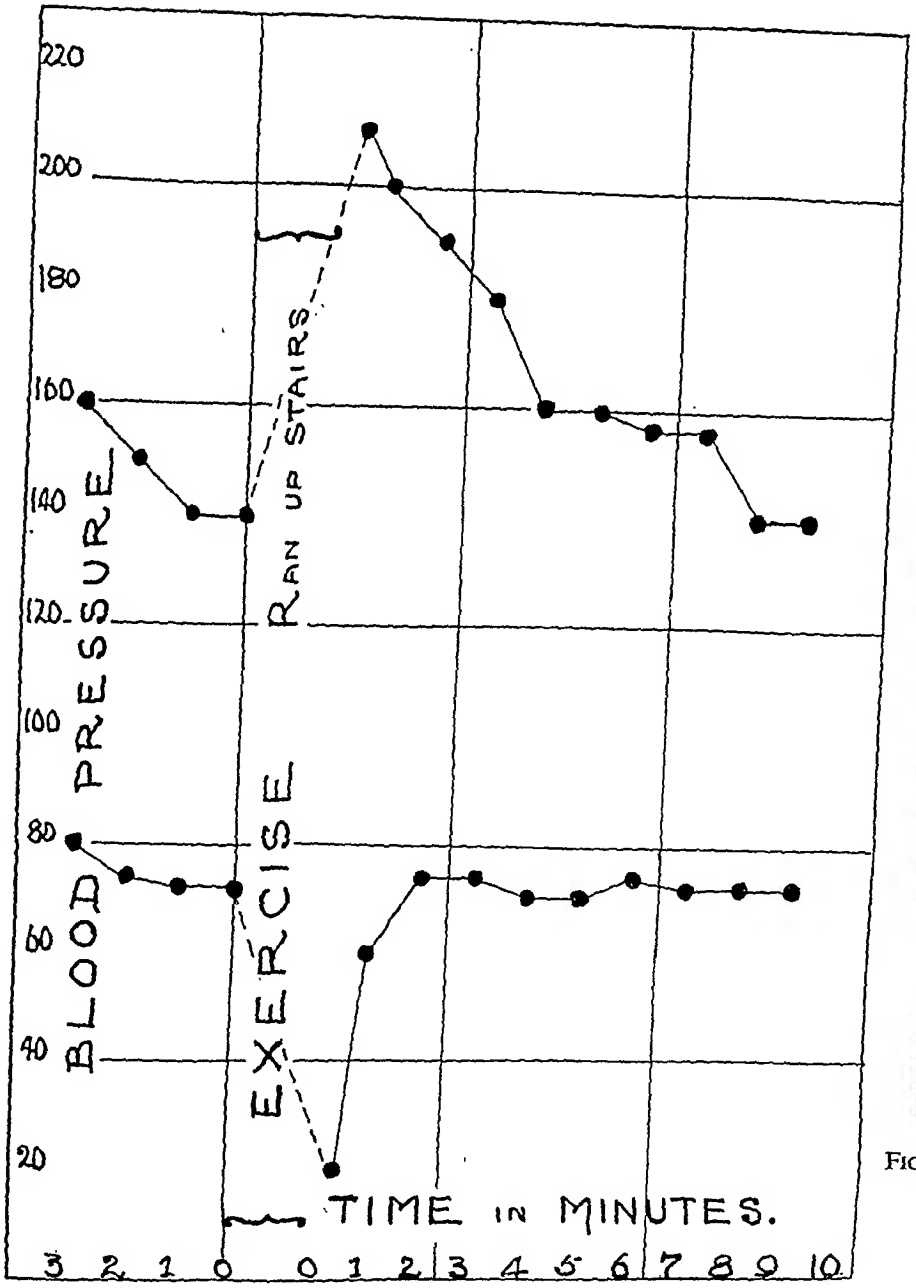

FIG. 3.—The response of the blood pressure to exercise in *P.D.A.* This man (Case 27) under resting conditions had normal blood pressure readings. After exercise there is an abrupt fall in diastolic pressure to 20 mm. with prompt recovery. This reaction is of diagnostic importance.

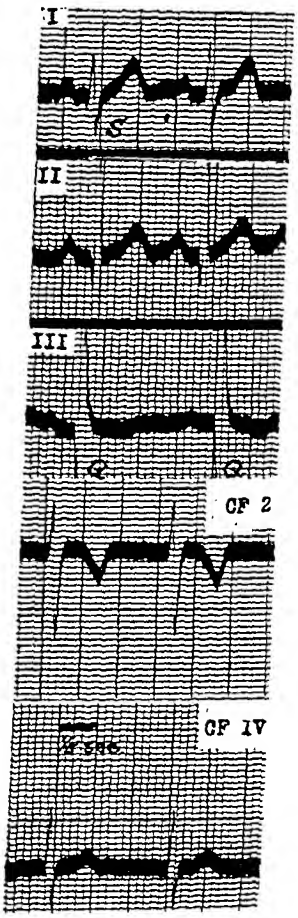

FIG. 4.—Electrocardiogram from Case 7, aged 5 years. At first glance it bears a superficial resemblance to right axis deviation, but on account of the prominent Q III the curves are classified as being of the diphasic type described by Katz (1937).

communication between aorta and pulmonary artery must be large and the peripheral resistance in the pulmonary, if not also in the general circulation, considerably reduced. Franck (1878) observed a paradoxical pulse, waning with inspiration, and Hochsinger (1891) an inequality in the amplitude on the two sides. On account of the possibility of a silent or minor degree of coarctation of the aorta—this and patency of the ductus being not uncommonly associated—blood pressure readings from the popliteal arteries are useful. Laubry (1930) has noted a difference in amplitude between the femoral and radial pulses significant of some slight coarctation. Corresponding brachial and popliteal pressures were obtained in eight patients under 10 years of age, all with frank signs of patent ductus arteriosus.

In every instance (except Case 7) the pulse pressure was greater in the leg than in the arm, thus excluding the presence of a significant degree of coarctation of the aorta (Table II). The diastolic pressure in the leg was higher than in the arm as in health, with the exception of two patients—Case 12, in whom at operation the slightest degree of isthmus narrowing was observed, and Case 19, in whom the difference (3 mm.) is perhaps too slight to be significant. In older patients coarctation can be

detected by radiological and other methods; but in patients under 10, blood pressure readings in the arm and leg are the only means likely to reveal a minor degree of isthmus stenosis, rib markings, for instance, being unusual in the first decade.

TABLE II

ARM AND LEG BLOOD PRESSURE IN 8 DUCTUS PATIENTS UNDER 10 YEARS

Case No.	Blood Pressure						Remarks
	Brachial artery			Popliteal artery			
	Syst. P.	Diast. P.	Pulse P.	Syst. P.	Diast. P.	Pulse P.	
7	88	44	44	104	?68*	36	No coarctation seen at operation.
8	96	54	42	124	64	60	No coarctation seen at operation.
11	105	45	60	125	60	65	No coarctation seen at operation.
12	132	72	60	152	66	86	Slight narrowing of isthmus seen at operation.
13	115	58	57	155	78	77	No coarctation seen at operation.
17	108	58	50	136	68	68	Not submitted to surgery.
19	82	45	37	135	42	93	Not submitted to surgery.
21	110	45	65	130	50	80	Not submitted to surgery.

* An end-point difficult to determine with certainty.

The Electrocardiogram. This is generally normal in patent ductus arteriosus (Schnitker, 1940). In my series left axis deviation was observed in seven patients (Cases 1, 3, 5, 6, 9, 15, and 18), all of whom were over 10 years of age. A diphasic form of complex, described by Katz (1937) was encountered on four occasions (Cases 3, 5, 7, and 18). Latent heart block (P–R interval 0·24–0·30 sec.) was observed in one patient (Case 4). Schnitker (1940) found only one instance of right axis deviation amongst seventy. A superficial resemblance to right axis deviation is shown in Fig. 4, but the curves are atypical and are classified, on account of the prominent Q III as diphasic. Fig. 5 shows left axis deviation, abolished by operation (Case 3), and Fig. 6 depicts a complex extrasystolic arrhythmia (Case 15)—an unusual finding as the heart is almost invariably regular in rhythm. No arrhythmias were observed by Schnitker (1940). It can therefore be said with Drawe (1937) that in diagnosis a normal or

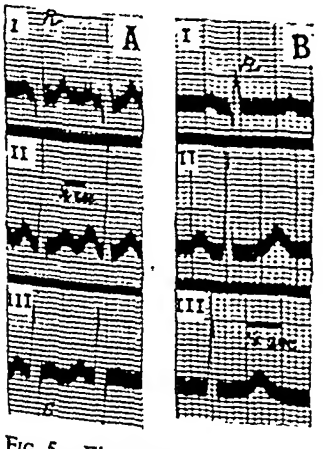

FIG. 5.—Electrocardiogram from Case 3. (A) Recorded before operation, shows well marked left axis deviation; (B) recorded 3½ years after surgical ligation of *P.D.A.*, shows loss of axis deviation, disappearance of S III, and diminution of R I.

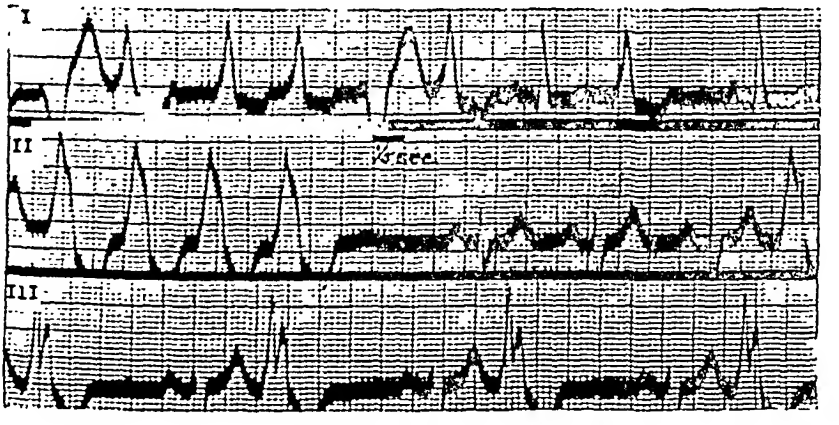

FIG. 6.—Electrocardiogram from Case 15 shows complex extrasystolic arrhythmia, with runs of coupled rhythm and occasional ventricular paroxysms—a most unusual finding in the presence of *P.D.A.*, in which the heart rhythm is almost always regular.

almost normal cardiogram favours a patent ductus arteriosus. Certainly the absence of right axis deviation is of help in excluding the presence of pulmonary stenosis, in which it is the rule (Alexander, Knight, and White, 1925).

Diagnostic Criteria. Particular emphasis has been placed on the importance of the auscultatory signs. To the trained ear diagnosis is simple, but even in the absence of the pathognomonic Gibson murmur the diagnosis can still be established with some justification if other signs are present. Amongst these, in order of importance, are: (1) an increased size and excursion of the main trunk of the pulmonary artery on radioscopy, (2) an increased pulse pressure at rest or induced or aggravated by the exercise test, and (3) a long, harsh systolic murmur maximum below the inner end of the left clavicle. This bruit in a child or young person, particularly when accompanied by a reduplicated or accentuated second pulmonary sound, should always arouse suspicions. The other physical signs—the thrill that accompanies the rougher murmurs, Gerhardt's ribbon dullness (an unreliable clinical sign of pulmonary artery dilatation incapable of revealing the minor degree of enlargement) and the pulsus paradoxus—are of much less importance as they are only found when the essential signs enumerated above are so striking as themselves to make the diagnosis obvious.

Differential Diagnosis

Reference has already been made to certain aspects of differential diagnosis. It is worth emphasizing that both pathological statistics (Bullock, 1939) and clinical experience indicate that after the first year of life has been passed other congenital cardiac defects are seldom found to accompany patent ductus arteriosus. Abbott's (1936) studies indicate that when the flow of blood through the ductus is a compensatory phenomenon for some other major congenital flaw, cyanosis is the almost invariable rule. Such defects as bicuspid aortic valves, or even patency of the interventricular septum, which may pass undetected, are not contra-indications to ligation. On the other hand, the failure to recognize the presence of a coarctation of the aorta is more regrettable. Ligation done in the presence of multiple defects cannot be expected to produce as satisfactory results. It may indeed prove harmful.

The congenital heart lesions likely to cause confusion are those accompanied either by basal systolic murmurs or by enlargement of the pulmonary artery. A harsh systolic murmur maximum in the second left space without cyanosis or clubbing and accompanied by a distinct second pulmonary sound, makes the presence of a congenital pulmonary stenosis most unlikely, for as pointed out by Muir and Brown (1932) in this latter condition the pulmonary second sound is as a rule weak or absent, although an accentuated sound has been observed on occasions (Eakin, 1929). If in doubt the fall in diastolic pressure induced by an exercise test will favour a patent ductus. Radiological examination is also helpful, attention being directed to the size and shape of the heart and the vigour and extent of the systolic excursion. Exaggeration of the cardiac pulsation occurs in a number of conditions. It is found in hyperthyroidism, in which the heart action has been described as "jittery" in character and affecting all the chambers, and also in aortic regurgitation, which imparts a distinctive rocking movement to the heart as a whole, with increased pulsation in the aortic notch (Donovan, 1943).

On the other hand, the enlargement of the pulmonary artery and its branches, so characteristic of auricular septal defect, may give rise to difficulty if the Gibson murmur is obscure or doubtful. This is accompanied by right ventricular hypertrophy, a shadow of the *cœur-en-sabot* type, right axis deviation, low blood pressure, and an absence of the circulatory phenomena of a low peripheral resistance. Similar findings help to exclude Fallot's tetralogy, Eisenmenger's complex, and Lutembacher's syndrome, in all of which cyanosis is commonly found. Graham (1940) has described how an aneurysm of the ductus arteriosus may readily be mistaken for a mediastinal tumour. The clinical history, the response of the blood

pressure to exercise, and screen examination, should help in the differentiation, if the Gibson murmur is absent.

The differentiation of ventricular septal defect is based chiefly on the site of the murmur, maximum in the third or fourth left space, and the absence of notable pulmonary artery enlargement. Schnitker (1940) has noted the presence of a steep S wave in leads I and II, but this is not supported by Brown's (1939) findings in *Maladie de Roger.*

Congenital defects of the aortic septum, consisting in a communication between the first part of the aorta and the pulmonary artery, above or below the cusps, are most uncommon but give rise to signs almost indistinguishable from those of a patent ductus arteriosus. Brown (1939) points out that the continuous murmur of the aortic defect tends to be maximum a little lower in the chest than the Gibson murmur. It is also louder, coarser, and more superficial, and the heart itself tends to be larger than that commonly found in the presence of uncomplicated patent ductus arteriosus. Cases of this type have been described by Fraentzel (1866) and Oberwinter (1904). One case has been explored in mistake for a patent ductus arteriosus but the surgeon had the good judgment to retreat without attempting ligation (Shapiro and Keys, 1943).

From acquired lesions—rheumatic or syphilitic—difficulty in differentiation seldom arises, though if the humming-top murmur is unusually faint and the diastolic element predominates and is, as sometimes happens, conducted down the sternum, some confusion may well arise. The site of maximum intensity, the dilated and pulsatile pulmonary artery, the vascular increase through the lung fields and the clinical history, should prove helpful in establishing the diagnosis of patent ductus arteriosus.

Functional and hæmic murmurs differ from ductal and other organic murmurs in their soft, blowing character. The benign murmur varies greatly with a change in the position of the patient, and with the phase of respiration. Hæmoglobin determinations, correction of the anæmia if present, and employment of the exercise test already described should readily differentiate these from the systolic murmur that commonly precedes the appearance of the fully developed ductal murmur.

In children a venous hum, without pathological significance, is occasionally heard in the root of the neck. It causes a continuous murmur, sometimes associated with a thrill (Hubbard, 1943), maximum above the clavicle. It is abolished by jugular compression, which has no influence on the Gibson murmur, and similarly a change of posture may cause this benign murmur to diminish or disappear altogether.

In general it may be said that difficulties in differential diagnosis seldom arise. Other congenital lesions can usually be excluded by simple clinical observations, and acquired heart disease presents as a rule a very different picture.

The Nature of the Defect

Although originally described by Galen as a short vessel uniting aorta and pulmonary artery, the ductus arteriosus has erroneously been associated with the name of Botallo. Franklin (1941) in a scholarly review of the classical literature has suggested an explanation for the mistake commonly perpetuated in the German writings. Misled largely as a result of an illustration inserted by van Horne in his edited edition of Botallo's complete works (1660), and confused by a superficial acquaintance with the original Latin text, subsequent writers have repeated the error. Botallo has no claim to the ductus and van Horne's illustration, reproduced in Fig. 7, is itself incorrect anatomically.

The ductus at birth is a short channel about 10 mm. in length and 5 mm. in width, wider indeed than generally assumed as it is equal to or greater in calibre than the aortic arch or pulmonary artery or descending aorta (Noback and Rehman, 1941). Its function was known to Harvey (1628), but it is only in recent years that exact observations have been made on the nature of the disturbance imposed on the circulation by its persistence.

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Figuræ primæ Explicatio.

A A A. Falx.
bbbb. Sinus falcis superior, seu longitudinalis, apertus.
C Osſiculum maximum. D. aliud prædicto minus.
e f Duo exigua oſſicula, ſatis tamen acuminata.

Figuræ ſecundæ Explicatio.

A. Cor.
B. Auricula dextra aperta.
C C. Vena Cava ſimiliter diſſecta.
D. Foramen venæ coronariæ
E. Foramen ovale, per quod ſanguis in auriculam ſiniſtram tenditur.
F. Valvula eidem foramini appoſita.

Figuræ tertiæ Explicatio.

A. Cor.
B B. Pulmones.
C C. Arteria aorta aſcendens.
D D. Arteriæ Truncus deſcendens.
E E. Arteria pulmonalis, ſeu Vena arterioſa dicta.
F F. Canalis à pulmonali arteria tendens in aortam.

venoſam, quæ & ſi fruſtra olim perquiſiverim, nuper tamen denuò eidem inquiſitioni me tradens, cor dividere occepi, ubi paulò ſupra

vas facilè reſupinaretur, quo ſanguis à vena cava cum impetu affluenti cederet quidem, prohiberet autem ne ſan-
guis rurſum in venam cavam reverteretur. Mox adjungit, ſuperat omnem admirationem, prædicti foraminis haud ita multo

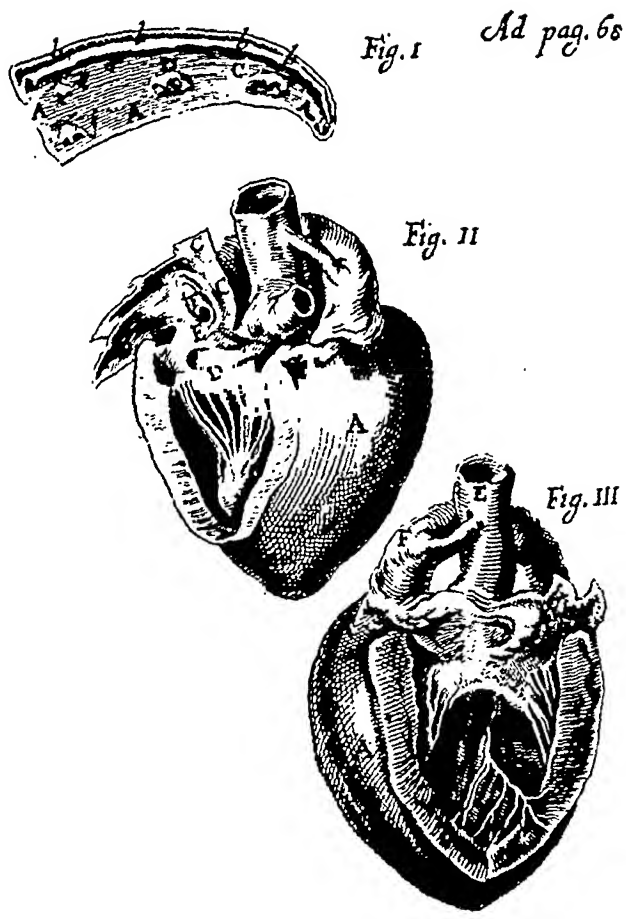


FIG. 7.—Van Horne's edition of Botallo's complete works (1660) contains this illustration inserted by the editor and not included in Botallo's original text. Botallo did not describe the ductus and the structure depicted in van Horne's illustration is anatomically incorrect.

From aorta to pulmonary artery there flows through the ductus a continuous stream of blood, often in great amount, which passes through the lungs to return immediately to the left ventricle and thereby complete a valueless short circuit. The leak from the aorta results in a low diastolic pressure, imposes an added burden on the left ventricle, and by increasing the pressure in the pulmonary artery adds also to the work of the right ventricle. The pulmonary artery dilates throughout its distribution, the lungs become increasingly vascular, and if the leak be sufficiently great, the circulatory phenomena in the periphery come to resemble more and more closely those of aortic regurgitation. Depletion of the general circulation is said to account for the common state of subnutrition and for the child's failure to thrive.

The careful physiological studies of Keys and Friedell (1939), Keys, Friedell, Garland, Madrazo, and Rigler (1940), Eppinger, Burwell, and Gross (1941), and Leeds (1942) have proved most illuminating. It has been demonstrated that the flow through the ductus can be very large, up to 50 per cent or more of the left ventricular output. The right ventricle receives the peripheral venous return which is passed through the lungs to the left side of the heart. The pulmonary artery is therefore filled from two sources. It receives the venous blood on its way to the lungs and also an arterial supply shunted from the aorta via the patent ductus. Consequently the lung vessels handle perhaps 50 per cent more blood than in health, all of which is returned to the left ventricle. The output of the two ventricles is therefore unequal, the left exceeding the right by the volume of blood accepted by the ductus and pulmonary artery.

It is very remarkable that the additional work imposed on the left side of the heart does not result in more serious signs of myocardial insufficiency and a greater degree of ventricular

hypertrophy. A peripheral arterio-venous fistula of equal size, uniting femoral artery and vein, imposes a greater burden upon both ventricles and leads to a great increase in heart size. The explanation of the difference is probably to be found in the nature of the " venous " side of the fistula. In the case of the patent ductus, constriction of the finer divisions of the pulmonary artery constitutes an area of peripheral resistance which effectively limits the blood flow through the ductus by maintaining a degree of pressure in the pulmonary artery. In the usual peripheral arterio-venous fistula the blood escapes readily into the capacious venous system at low pressure, and against little resistance. This leads to progressive dilatation of the heart and of the entire circulatory bed through which the short-circuited blood flows. It may be suggested that in the presence of a patent ductus arteriosus the finer subdivisions of the pulmonary artery by imposing a degree of peripheral resistance in the lesser circuit effectively protect the left ventricle from overstrain. Hypertrophy of the media of the finer pulmonary arterioles is sometimes demonstrable. Bettinger (1941) believes that hypertrophy of the right ventricle with constriction of the lung arteries are compensatory phenomena, overloading of the pulmonary system being thereby reduced to a minimum. For a discussion of the circulatory dynamics of peripheral arterio-venous fistulæ, which have much in common with the disturbance of the circulation attributable to a patent ductus, reference may be made to the papers of Lewis and Drury (1923), Harrison, Dock, and Holman (1924), and Holman (1940*a*).

Pathological statistics regarding the size of the patent ductus arteriosus are misleading, as the channel shrinks in a remarkable way after death. At operation it is usually found to be a large vessel, often as wide as the arch of the aorta. In length it is relatively shorter in adults than in children but is usually cylindrical in shape, thus permitting ligation. Gerhardt (1867) has described various types of patent ductus arteriosus : (1) the cylindrical, (2) the funnel-shaped with the apex towards the pulmonary artery, (3) the important window-type which may be better likened to the artificial stoma of a gastro-enterostomy (this is not amenable to surgical ligation), and (4) the aneurysmal form. Keys and Shapiro (1943) collected 10 examples of the fistula-like opening between the pulmonary artery and aorta in their review of 60 fatal cases. Of Jager and Wollenman's (1942) 71 autopsy specimens, 3 obtained from infants were of the window type. So far there is no means of recognizing with certainty the type of ductus likely to be encountered at operation, though angiocardiography may yet provide the help required.

Present Investigation

All the patients composing the present series have been personally examined and seen repeatedly during the past four years. A few others have been excluded for various reasons, chiefly the impossibility of following their progress. Two patients seen in hospital some years before the present studies have re-attended and have been included, so that the longest period of observation extends to 14 years (Case 16). The shortest period is 2 months (Case 28).

This series is composed of 28 patients, 15 females, and 13 males—a higher proportion of males than usually found. It is universally agreed that patent ductus arteriosus is more common in the female sex. Keys and Shapiro (1943) in an analysis of causes of death found 14 men and 46 women. Donovan (1943) reporting the cases under the care of Gross verified surgically found 17 males and 33 females. Keys and Violante (1940) observed 6 males and 17 females. Muir and Brown (1932) based their report on 7 males and 13 females. The condition of patent ductus arteriosus is therefore about twice as common in females as in males.

The Age Distribution. The average age for the whole series of 28 is 15 years, the oldest survivor at the present time being now 49 and the youngest 4 years. There is general agreement that patent ductus arteriosus is more frequently met in the first ten years of life. Its

recognition after 20 or 30 is unusual and in sharp contrast to another and perhaps more common congenital disease—auricular septal defect—which comes under observation as a rule in middle or later adult life. Comparative figures are presented in Table III, which shows the age distribution of two series, one personally observed and the other collected. The 25 examples of auricular septal defect were observed over the four-year period during which the 28 cases of patent ductus arteriosus were studied.

TABLE III

AGE DISTRIBUTION OF PATENT DUCTUS ARTERIOSUS AND AURICULAR SEPTAL DEFECT

Author	Age groups							Total
	0–10	11–20	21–30	31–40	41–50	51–60	61–70	
	Patent ductus arteriosus							
Goodman (1910)	11	5	6	6	3	3	0	34
Muir and Brown (1932) ..	8	11	1	0	0	0	0	20
Gilchrist (1945)	14	8	3	1	2	0	0	28
Total for each age group ..	33	24	10	7	5	3	0	82
Percentage of series	40	29	12	9	6	4	0	
	Auricular septal defect							
Bedford, Papp, & Parkinson (1941)	3	7	14	10	16	3	0	53
Gilchrist (unpublished)	1	3	5	6	4	3	3	25
Total for each age group ..	4	10	19	16	20	6	3	78
Percentage of series	5	13	24	20	26	8	4	

Contrasting the incidence of these two, it is evident that patent ductus arteriosus is recognized at an earlier age than auricular septal defect. Of the former, 70 per cent are recognized before 20; whereas the reverse holds true for the auricular defect, 82 per cent coming under observation after 20 years of age.

There are probably several explanations for this finding. The routine examination of school children permits the ready detection of the relatively simple physical signs of patent ductus arteriosus, whereas auricular septal defect is latent and easily overlooked in youth and produces its ill-effects and more urgent symptoms in later life, when the physical signs are gross, the X-ray picture distinctive, and the diagnosis only then relatively straightforward. That this is not an entirely adequate explanation for the distribution of the ductus cases is proved by the fact that it is extremely difficult, if not impossible, to collect a series of adults with frank signs of uncomplicated patent ductus arteriosus. The problem may be presented from a different angle. Suppose, for instance, that auricular septal defect was a condition easy of recognition in childhood. It is then still logical to assume that patients so affected would continue to present themselves for treatment in the later age groups as they do at present. Patent ductus arteriosus, though recognized in youth, is not a condition which runs a course comparable to auricular septal defect. After the ductus cases pass from the care of the pædiatrician their numbers apparently decrease to such an extent that they are seldom recognized either in the wards or in the post-mortem room.

The scanty number of adults with patent ductus might be attributed to the clinician's failure to recognize the less characteristic signs. A further possibility is that by the time the older patients present themselves for treatment the usual diagnostic features may have altered, diminished in intensity, or even disappeared completely. Well-authenticated cases are on record where experienced observers have failed to detect the characteristic murmur and the diagnosis was only established at autopsy. Duroziez (1862) reported the death of a man, aged 40, in congestive heart failure in whom at autopsy a patent ductus admitting a large pea was found, no murmurs having been heard during life. Foulis (1884) noted in his patient that the murmurs present disappeared twenty-six days before death. Keys and Shapiro (1943) had a patient under observation for ten days in whom at autopsy the ductus was 2 cm. long and 1·5 cm. wide, but no murmurs were heard.

It is therefore evident that, in the presence of congestive heart failure, reliance cannot be placed on the auscultatory signs alone. To do so implies that the diagnosis during the terminal illness may be missed.

Similarly, the small number of adult cases recorded by the pathologist demands an explanation. White (1926), for instance, could only discover 7 instances of patent ductus arteriosus in patients over the age of one year amongst 5000 consecutive autopsies, and of these 3 were adults. Two possibilities arise. Either pathologists are failing to look for the lesion systematically, or else it may be that as the patients grow older the ductus closes spontaneously and all evidence—clinical and pathological—of the original defect disappears. That such an event can occur is evident from my Case 22, but it must be exceptional. Otherwise clinicians could hardly fail to have made the observation repeatedly. The problem of the scanty number of adult patients is not yet solved, but there is reason to suppose that it will be simplified if the clinician will put greater trust in the more stable physical signs—the enlarged pulmonary artery and the high pulse pressure—and less in the characteristic murmur, which is apt to disappear when congestive heart failure is present. Similarly, the careful inspection by the pathologist of the region of the aortic isthmus as a routine procedure in every case would do much to simplify the problem of the lack of known examples of patent ductus arteriosus in the adult population.

The 28 patients in this series have been divided into two groups. Group A is a control series of 14 patients in whom for one reason or another surgery was considered unnecessary or undesirable. Group B is composed of 14 patients submitted to surgical ligation. Their progress was observed for varying periods of time before surgery was undertaken, 9 years in one instance, and so far a maximum of 45 months and a minimum of 6 months have followed ductal occlusion.

(A) Control Patients (Cases 15 to 28)

The 14 patients in this group consist of 9 females, ranging in age from 5 to 34 years, and 5 males of from 6 to 49 years. The average age in this group is 20 years. Certain details are shown in Table IV. Two of the 14 patients have died—Case 23, at 42 of subacute bacterial endarteritis with congestive heart failure, and Case 24, at age 15 of acute poliomyelitis with respiratory paralysis.

Fatal Cases. From a study of reported cases Keys and Shapiro (1943) find that 42 per cent of patent ductus arteriosus deaths are the result of subacute bacterial endarteritis of the pulmonary artery and ductus. There is reason to believe that this infection is even more common. It masquerades under various erroneous diagnoses, mostly with a pulmonary background, for example, miliary tuberculosis, tuberculous pneumonia, sulphonamide-refractory pneumonia, mitral disease with pulmonary infarction, or simply as septicæmia. In Horder's (1940) opinion a number of infected ductus patients find their way to sanatoria and remain undiagnosed to die of septicæmia, anæmia, and congestive failure. Up to 1932 only 23 reported cases of infective endarteritis could be collected (Fischer and Schur, 1932).

The diagnosis is important as surgery promises now at least a 50 per cent rate of recovery, whereas on medical measures the disease is uniformly fatal. No patient with a patent ductus should be allowed to run an unexplained fever for as long as 10 days without blood cultures and radiograms of the lungs for infarcts. Surgical ligation is the only treatment to consider. In Case 23 we decided that the opportunity for ligation had passed, the local infection being so extensive and the prospects so poor that surgery after thirteen months of septicæmia offered no hope of cure. Subacute bacterial infection can occur at any age, though most uncommon in the first decade (Hubbard, Emerson, and Green, 1939) and strikes the apparently symptomless as well as the more handicapped patient without warning. If it is, as statistics would suggest, a leading cause of death in patent ductus arteriosus, it is curious that the general hospitals are not more familiar with it and that it should still be regarded as a rarity in pathological and clinical experience. My personal experience is limited to three cases seen during the past four years.

Case 24 is instructive for another reason. This girl died of an intercurrent infection in another hospital. It was natural that in view of the diagnosis of poliomyelitis the pathologist should devote particular care to the central nervous system. Although the diagnosis of patent ductus arteriosus was

TABLE IV

FEATURES OF 14 CONTROL PATIENTS (GROUP A)

Case No., Sex, and Age	Occupation	Date of examination	Physical capacity	Heart size		Blood pressure		Remarks
				m.t.d. (mm.)	P.A.I.	Syst.	Diast.	
15. m. 45	College lecturer	11/3/40 21/7/44	2 3	160 185	80 89	168 180	88 105	A neurotic man. Highly irregular pulse (Fig. 6). Slight deterioration in health.
16. f. 20	Housework	6/10/30 24/3/41 27/6/44	2 2 2	— 130 127	— 64 66	110 132 140	50 60 72	Fatigue. Working as table-maid. At sixth month of third pregnancy. Good health. Busy capable housewife and mother of 3 children.
17. f. 5	At school	17/11/41 13/12/43 26/7/44	2 2 2	95 — 98	55 — 57	108 110 106	68 64 64	Fatigue. Pulmonary systolic. P_2+. Good health. Gibson murmur heard for first time. Murmur more intense. Thrill now felt. Health good.
18. f. 24	Housework	1/3/43 30/9/44	2 3	148 146	75 72	120 130	30 50	In last month of sixth pregnancy. Tired. Six children. More distressed than during pregnancy.
19. f. 5	At school	6/12/43 20/9/44	1 1	79 85	45 46	96 86	56 42	Small child, retarded development. *No symptoms.* Health satisfactory. Heart enlarging.
20. m. 4	At school	11/4/42 13/10/44	1 1	108 114	53 55	95 110	45 45	Harsh pulmonary systolic. Faint ductal murmur. I.s.q.
21. f. 4	At school	25/10/43 19/6/44	1 1	93 —	52 —	110 110	50 45	Good health. No symptoms. Definite signs. I.s.q.
22. m. 5	At school	20/8/42 26/4/44	1 1	101 85	55 54	76 108	?40 55	Definite signs with Gibson murmur. Ht., 42 in.; Wt., 41 lb. (Fig. 8A). Murmur absent. Ductus closed. Perfect health. Ht., 48 in.; Wt., 50 lb. (Fig. 8B.)
24. f. 14	At school	26/2/42	2	111	60	112	54	Readily fatigued. Died 9/8/42 of acute poliomyelitis after 4 days' illness. Pathologist failed to report on state of ductus, etc.
25. f. 5	At school	26/4/44 5/7/44	2 2	92 —	50 —	100 90	?60 62	Liable to "faints." Weak Gibson murmur. Gibson murmur almost inaudible. ? *Ductus closing.*
26. f. 19	Telephonist	4/5/44	1	110	70	136	76	Fatigue and anxiety. A neurotic girl.
27. m. 37	Fisherman	9/8/44	3	118	85	140	72	Exertional pain and ready fatigue. *Mildly neurotic* since discharge from Royal Navy four months ago after 3 years on active service. Slight deterioration in physical capacity.
28. m. 24	Bus driver	26/7/44	2	123	80	118	46	Slight dyspnœa and fatigue all his life. In semi-recumbent position a distant, slow Gibson murmur detected in third left space. Able for work. Since discharged from Army after 2 years' service a little neurotic.
One Case of Subacute Bacterial Endarteritis								
23. f. 42	Schoolteacher	31/3/42	5	Enlarged		—	—	Died 17/4/42 after a year's *illness.* Multiple peripheral and pulmonary infarcts, congestive heart failure, and exhausted state did not justify recommendation for surgery.

The age stated is that at the time of the first examination.

The physical capacity of each patient has been assessed according to a numerical scale at the corresponding date of examination. Grade 1, no limitation of physical activity; 2, slight limitation and 3, moderate limitation on heavier exertion; 4, ordinary activity causes distress, often with a trace of œdema at night; 5, mild congestive heart failure; 6, advanced congestive heart failure. Slight deterioration was detected only in three patients—Cases 15, 18, and 27.

Heart size is recorded as the maximum transverse diameter (m.t.d.) in mm. in the teleradiogram. The pulmonary artery index (P.A.I.) is employed as a measure in mm. of the size of the pulmonary artery (Evans, 1943).

The blood pressure figures are the lowest of several readings recorded on the date mentioned.

made beyond doubt clinically and radiologically by at least three independent observers, the pathologist omitted to look for the ductus and made no reference to it in his report. It is certain that many autopsies fail to disclose the patent ductus because of the habit of removing the heart by severing the great vessels proximal to the aortic isthmus. As long as these crude methods continue, so long will pathological help in solving the problem of prognosis remain unavailing. The aortic isthmus is the most neglected region in cardiovascular pathology. Lack of numbers in pathological statistics may well be accounted for by a failure to seek and record the lesion in adults. The attention of the pathologist directed to the region of the ductus in every case of obscure fever or of congestive failure in adults, whether the physician suspects such possibilities or not, will prove of inestimable help in the solution of the problem of prognosis in patent ductus arteriosus.

Progress of Survivors. From a consideration of the ease with which symptoms are induced it can be said that no physical deterioration has been observed, nor does their history

suggest its development in the years before coming under our observation, in Cases 16, 17, 19, 20, 21, 25, 26, and 28—that is, in 8 of the 12 remaining patients. The capabilities of some of these patients in relation to their age and heart size are worthy of note.

A married woman now aged 34, observed with particular attention throughout her last pregnancy and labour which she accomplished without distress, is the mother of three children. She is a busy housewife, able for all her work and shows no evidence of increasing cardiac enlargement or of physical deterioration (Case 16). Similarly, Case 28, a soldier aged 24, discharged from the army after 18 months' service, is able for his work as a bus driver. Cases 17, 19, 20, 21, 22, and 25, are children, who though perhaps a trifle retarded in physical development are in reasonably good condition, fit for school, and up to date have shown no deterioration in the year or two during which they have been under observation.

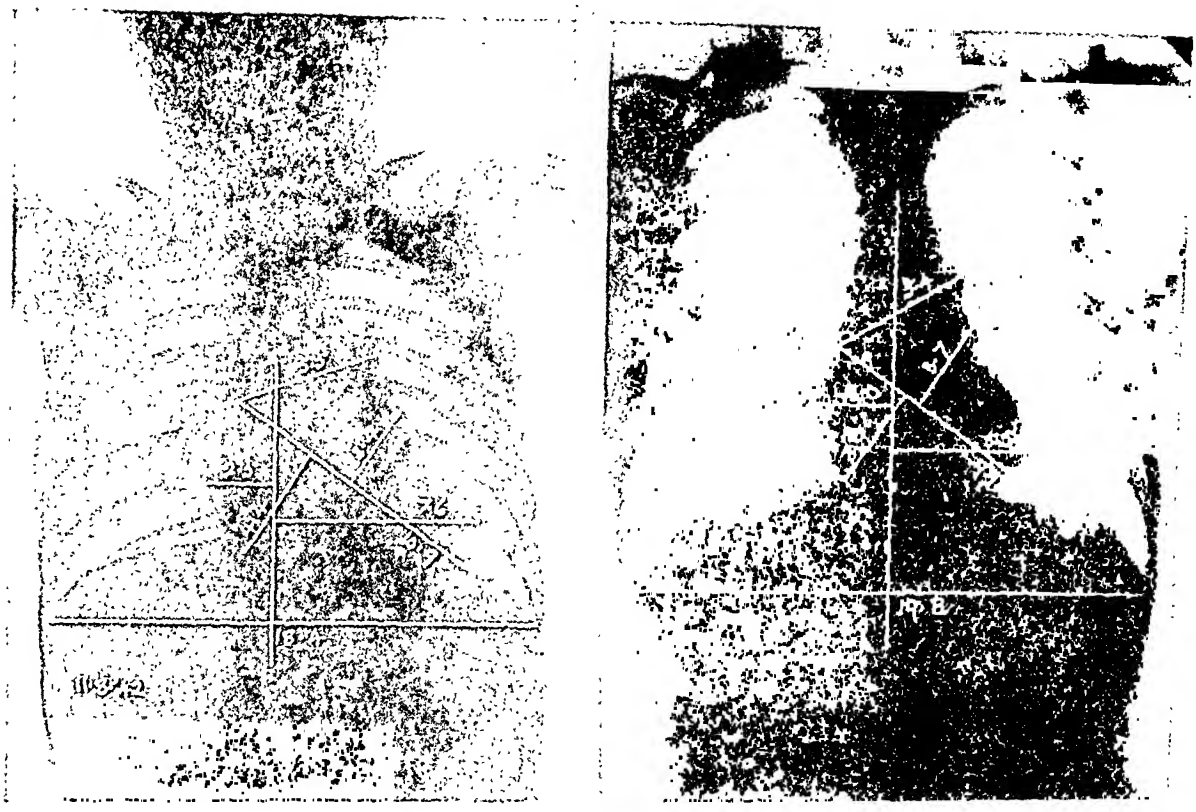
On the other hand, Cases 15, 18, and 27 have deteriorated slightly. Case 15 is now aged 49, a neurotic subject, but his response to effort is genuinely impaired, his heart is showing evidence of increasing left ventricular hypertrophy, and he has a highly irregular pulse (Fig. 6). Case 18, a married woman of 26, has had six children, all alive and well, with no unusual difficulties in pregnancy or labour. Recently her reserves have begun to diminish and in her physical capacity there is slight deterioration. Similarly, Case 27, a fisherman, aged 37, discharged after three years' service with the Royal Navy, now finds his work more exhausting but keeps fit for duty: he shows a slight limitation of physical capacity. No enlargement of the heart is demonstrable in either Case 18 or 27.

In the group as a whole a distinct neurosis was present in four patients. Most advanced and most incapacitating in Case 15, it was also a handicap in Case 26, being based originally on an incorrect diagnosis, and to a less extent in Cases 27 and 28, both of whom had been discharged from the services on account of the accidental discovery of physical signs. Brown (1932) noted neurotic tendencies in 2 of his 20 patients.

Spontaneous Closure of the Ductus. One remarkable patient (Case 22) in this group demands special emphasis. This boy at the age of 5 had an enlarged heart with a whirling Gibson murmur at the usual site. By the age of six and a half the murmur had disappeared, the heart had returned to normal, and the boy had grown and developed out of all recognition. Fig. 8, A and B, make a striking contrast. Spontaneous closure in an active, growing boy has seldom been observed, and so far as I have been able to discover, has not previously been substantiated by radiological proof.

Balfour's (1898) report is not very convincing. He describes how after a lapse of 15 years a murmur originally attributed to a patent ductus had disappeared. The patient was "a young lady . . . there was neither duskiness of complexion nor any murmur left. Evidently the ductus arteriosus had completely closed as it is occasionally known to do even late in life." Williams (1909) mentions a child "with a loud and prolonged murmur of roaring character continuous through the whole cycle. After 2½ years it had been replaced by a faint systolic bruit." The conclusion that gradual obliteration of the ductus arteriosus had taken place, or was in progress, seems amply justified from the scanty facts. Jacobi (1914) makes the interesting statement that, after observing a child once or twice a year from infancy, the ductus closed about the age of 9 or 10, "the murmur getting less and less marked until it finally disappeared." Keys and Shapiro (1943) refer briefly to two remarkable patients under their observation, who have recently shown evidence of spontaneous closure and disappearance of all signs of any lesion.

Spontaneous closure of the ductus can occur, presumably at any age, though to judge from clinical experience and the scanty reports, it must be very rare. Presumably the process is more likely to occur when the ductus is small, as in childhood, and before dilatation of the pulmonary artery has developed to a substantial degree and before degenerative atheromatous changes, with loss of elasticity of the vessel walls, have occurred. It is evidently a gradual process. It seems possible that closure might have been excited by the alterations in intra-pulmonary pressure, the accompaniment of the severe attack of whooping cough from which this boy suffered. On the other hand, several other children in this series have suffered from whooping cough without any change in the character of their physical signs. Whatever the mechanism, the fact remains that spontaneous closure of the ductus, up to the age of 10 or even older, is a possibility to be considered.



A B

FIG. 8.—Spontaneous closure of the ductus between the age of 5 and 6½ years. Case 22. (A) Radiogram of August 1942 shows considerable cardiac enlargement. The m.t.d. is 10·1 cm. and P.A.I. 5·5 cm., with distinct prominence of pulmonary arc and increased vascular markings, particularly in the upper and mid-zones of both lungs. The physical signs of patent ductus were well-marked. (B) The same child in April 1944. No physical signs of *P.D.A.* Gibson murmur no longer heard. Note striking decrease in size of heart, affecting chiefly the left ventricle, the clear lung fields and the growth of the thorax. The m.t.d. is now 8·5 cm. as compared with 10·1 cm. 20 months previously.

Summary. To summarize the essential features of this group, observation of the 14 patients has shown no deterioration in 8, slight deterioration in 3, death in 2 (one from sub-acute bacterial endarteritis and one from intercurrent infection), and recovery (spontaneous closure of the ductus) in 1—a boy of 6½ years. It is noteworthy that the majority lead normal active lives. Two women have married and have borne families without cardiac incapacity. From such facts as these it might be argued that surgical intervention has little to offer and that, reaching early adult life, many patients keep remarkably free of incapacitating symptoms, and are capable of leading useful lives.

THE OBJECTS OF SURGICAL LIGATION

Few will quarrel with the surgeon's intentions. He seeks to restore the integrity of the circulatory system embarrassed by an arterio-venous fistula of a peculiar type. Holman (1940*a*) has pointed out how in peripheral arterio-venous fistulæ abolition of the leak results in a prompt reversal of the circulatory changes, a permanent elevation of the diastolic pressure due to elimination of the focus of low peripheral resistance being one of the most notable findings. On this there follows a gradual reduction in the size of the heart and of the vessels to and from the previous site of the fistula. This is attributed to a reduction in the volume of blood traversing that part of the circulatory bed common to the primary and secondary circuits.

Applying these results to patients in whom the patent ductus arteriosus has been ligated, it is reasonable to expect a reduction in the size of the heart, chiefly on the left side, and of

the pulmonary artery and all its branches throughout its distribution. By sealing the leak the work of the heart is reduced and circulatory efficiency correspondingly improved. In contrast to many other pathological states, therapy does not merely arrest the disease: it activates a reversible process as a result of which myocardial tone is fully restored. There is therefore every reason to suppose that ductal occlusion will prevent the development of congestive heart failure to which these people are believed to be particularly liable. The harmful effects of persistent patency of the ductus are bodily under-development and malnutrition, with a low-grade circulatory incapacity leading to congestive heart failure. Surgery can correct these tendencies.

Sufficient time has not yet elapsed to judge of the influence of surgical ligation on the prevention of bacterial endarteritis of the ductus or pulmonary artery. There is every reason to suppose that the risk of this most serious complication will be greatly reduced in the future. Our present conception of the nature of this disease is based on the belief that the infection develops at the site of intimal damage. Exposed to a high pressure jet from the ductus, and with swirling blood currents constantly impinging on its walls, the pulmonary artery is submitted to excessive strain which over a period of years leads to intimal thickening, to cholesterol deposition, and ultimately to the formation of the typical atheromatous plaques. These occur at the orifices of the ductus but are most marked on the wall of the pulmonary artery, lying immediately opposite the orifice of the ductus. It is at this site that the infection becomes localized and vegetations most profuse (Fig. 9). It is reasonable to suppose that ligation of the ductus in early life will prevent the local degenerative vascular changes that predispose to bacterial endarteritis.

On the other hand, it has been suggested that at each end, adjoining the aorta and pulmonary artery, the remnants of the ligated ductus will form crypts which might afford a lodging for a blood infection. Only a few autopsies have been made after successful ligation of the ductus so that conclusive evidence of the nature of the obliterative process at the former ductal orifices is not available, but Tubbs (1944) in one patient (his Case 9) found four months after surgical occlusion that the ends of the ductus, which itself had been completely obliterated, were represented by no more than shallow depressions, with smooth floors devoid of thrombi. It would seem that the crypts produced by ligation of the ductus are unlikely to persist. Hence the risk of infection should be greatly reduced.

The rationale of ligation in the presence of an acute or subacute endarteritis of the ductus arteriosus and pulmonary artery is a difficult problem. It has been discussed by Touroff (1942*a*) and Tubbs (1944), the consensus of opinion being that a number of factors must play a part in the eradication of the disease by this means. Boldero and Bedford (1924) suggested that the rarity of bacterial endocarditis on the right side of the heart might be accounted for by the reduced oxygen content of the venous blood. Ligation of the infected ductus will deprive the local infection of arterial blood and reduce the wear and tear to which the pulmonary artery and its contained vegetations are exposed. Touroff (1942*a*) emphasizes the importance of the cessation of the forceful blood-flow through the ductus whereby fragmentation of the infected clot is greatly reduced. As a result of ligation he believes that the lung capillaries, now less dilated and fed by a blood-stream at a reduced pressure and volume, are able to filter off the few emboli that are formed. The rapidity with which the blood infection comes under control after ligation is very remarkable. For example, in one of the patients (his Case 6) reported by Tubbs (1944) 130 colonies of a *Strept. viridans* per c.c. were obtained before operation, whereas 37 minutes after ligation the blood grew 26 colonies, four hours after 8 colonies, seven hours after 5 colonies, and next morning only 1 colony per c.c. Presumably the lungs filter off the organisms and the vegetations heal by organization of the clot.

The ligation of the ductus was first suggested by Munro (1907). The first attempt by Graybiel and Strieder (1938) failed for technical reasons, and the patient died a few days later. It remained for Robert Gross of Boston to devise and perfect the trans-pleural approach, the

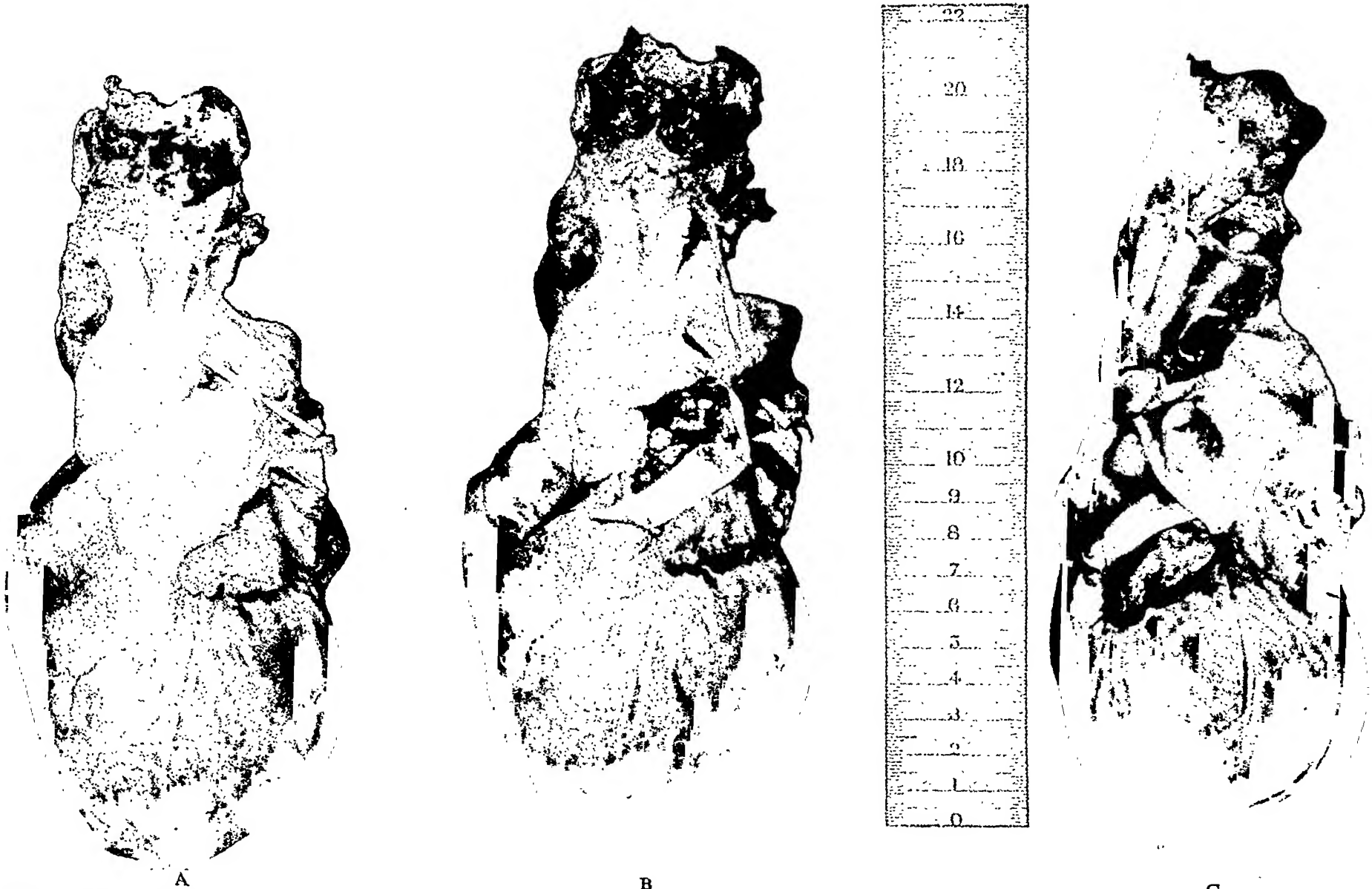


FIG. 9.—Patent ductus with infective endarteritis of the pulmonary artery. Case 14. (A) Photograph of heart. A marker has been inserted behind the ductus, which has contracted greatly as a result of surgical ligation and fixation. The ligatures have been removed. The enormous dilatation of the pulmonary artery is well shown. (B) The pulmonary artery has been opened in its long axis to reveal a mass of luxuriant vegetations, most profuse around and opposite the orifice of the ductus. A single tiny vegetation like a small wart is evident on one pulmonary cusp, the mass of vegetations and recent clotting in the pulmonary artery extending almost to this particular cusp. (C) The aorta has been cut across immediately distal to the left subclavian artery, and then thrown open to reveal the aortic orifice of the ductus. No vegetations are visible. A few patches of atheroma lie around the mouth of the ductus.

first successful ligation being reported by Gross and Hubbard (1939). The details of the Gross technique (1939*a*, 1939*b*) have been modified slightly, Touroff (1942*a*) in particular emphasizing the great advantages of subadventitial dissection on the arch of the aorta. Harrington (1943) recommends a posterro-lateral approach to the mediastinum in preference to the antero-lateral used by the majority of thoracic surgeons. Since 1939 the brilliant achievement of Gross has been repeated in various parts of the world. Shapiro and Keys (1943), with the co-operation of surgeons throughout the United States and Canada, were able to collect 140 cases. Of 107 non-infected cases ligation was completely successful in 81, and 9 patients died at or shortly after operation. Of 33 examples of subacute bacterial endarteritis, surgery was completely successful in 20, and 5 patients died at operation.

(B) Patients submitted to Surgical Ligation (Cases 1 to 14)

The 14 patients in this group consist of 6 females, ranging in age from 5 to 28 years, and 8 males of from 4 to 19 years. The average age of this group is 13 years. Four deaths must be recorded, two patients dying from subacute bacterial endarteritis, on which account surgery was undertaken (Cases 1 and 14), and two, non-infected patients, dying in the period after operation. One died from hæmorrhage from a torn ductus (Case 2); the other's death was attributed to a deep-seated mediastinal infection (Case 12).

The Infected Ductus. The work of Touroff (1940, 1942, 1943) and Tubbs (1944) indicates without a doubt the justification, indeed the absolute necessity, for recommending ligation of the infected ductus. The condition carries with it all the gravity of an ulcerative endocarditis. The clinical diagnosis is based on evidence of septicæmia, local signs of a patent ductus, and a patchy consolidation through the lungs, advancing and subsiding as fresh emboli are shed from the vegetations in the ductus or pulmonary artery. From even a limited experience of these patients I should like to suggest that a characteristic X-ray picture exists from which the physician or radiologist may make the diagnosis with confidence (Fig. 10). Absence of the fully-developed radiological appearances does not necessarily exclude the diagnosis but the chest films, revealing prominence of the pulmonary artery, progressive cardiac enlargement, and patchy consolidation throughout the lung fields, advancing here and subsiding there, must make a unique combination on which the diagnosis can be made. So far as the heart itself is concerned, the noteworthy finding is the rapid development of cardiac enlargement affecting chiefly the left ventricle, and increasing dilatation of the pulmonary artery. Other causes for enlargement of the pulmonary artery, such as auricular septal defect, are accompanied by right ventricular hypertrophy and are seldom if ever complicated by a local subacute infection. Great enlargement of the heart in the presence of a patent ductus is always suggestive of a bacterial endarteritis. The successive X-rays recorded at intervals of some weeks and reproduced in Fig. 10, are regarded as the characteristic sequence on which a diagnosis of subacute bacterial endarteritis of the pulmonary artery and patent ductus might be based. Similar X-ray findings were noted in Case 1 and are also evident in the illustrations of one of Touroff's (1943) patients (his Fig. 1, 3, and 6, Case 7). This radiological picture will not be found invariably. Indeed, surgical measures should be undertaken before multiple pulmonary infarcts exhaust the patient, increase the hazard, and complicate the approach to the ductus. Similarly, the chances of success are greater, the less dilated the heart. The accurate interpretation of the radiological findings should reduce the frequency with which the clinical diagnosis of an infected ductus is missed.

The first successful ligation of an infected ductus was done in December 1939 (Bourne and Tubbs, 1941). Since then Tubbs (1944) has reported recovery in 6 of 9 infected cases. Shapiro and Keys (1943) were able to collect the results obtained in 33 patients, including the 12 reported by Touroff (1943), of whom 10 survived operation and 7 recovered from the infection. Recovery was complete in 20 of the 33 patients. Blood cultures became sterile, often with surprising rapidity (Touroff, 1942*c*, Tubbs, 1944), the general condition improved

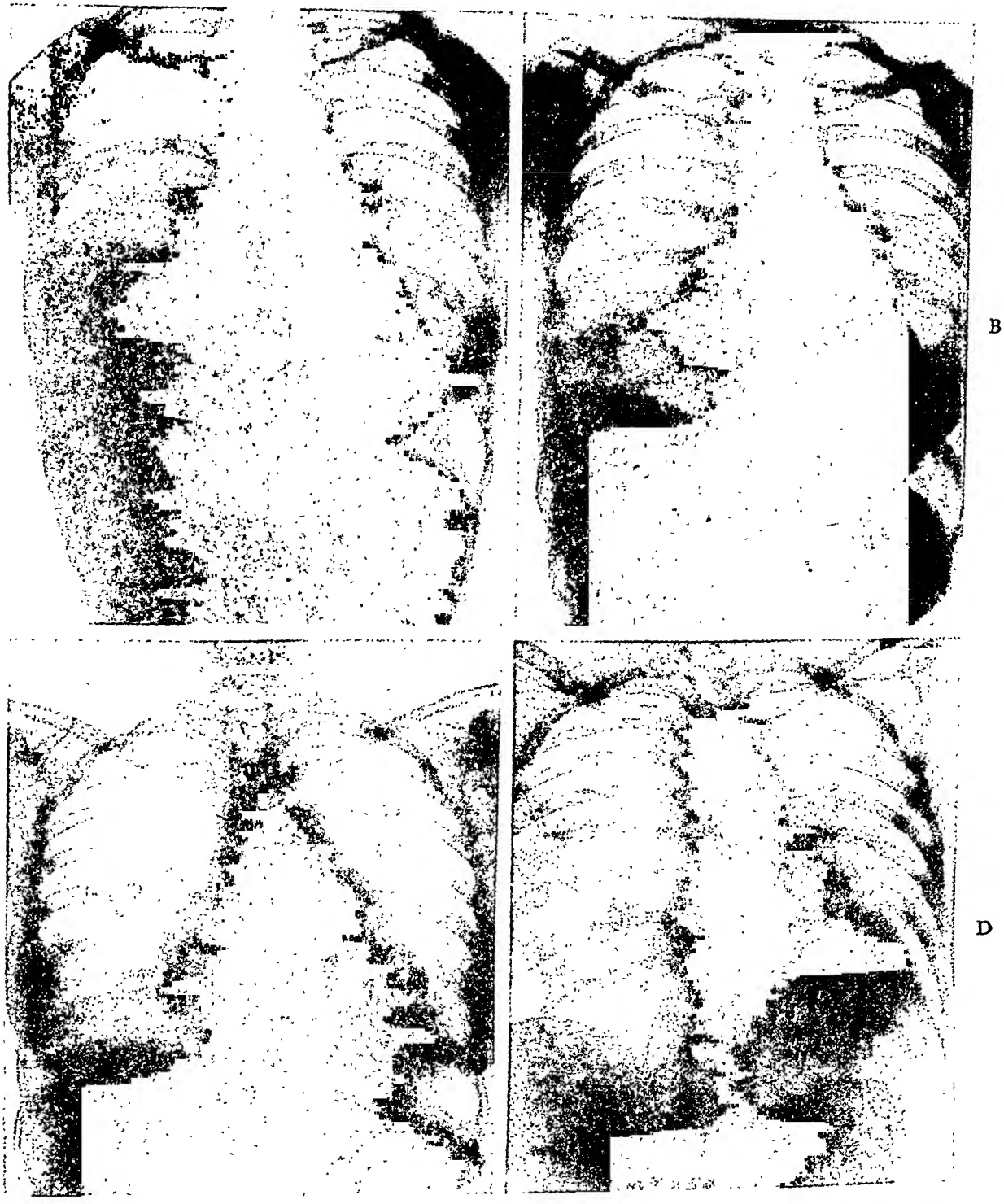


FIG. 10.—Radiograms in bacterial endarteritis. Case 14. (A) Teleradiogram 18/1/44. Enlarged heart, prominent pulmonary arc, P.A.I., 8·4 cm. Consolidation of varying intensity at right base. Increased vascularity of lungs. (B) Teleradiogram 1/3/44. Heart a little larger. P.A.I., 8·7 cm. Consolidation resolving at right base, a little now at left base. (C) Teleradiogram 11/4/44. Heart larger. P.A.I., 9·4 cm. Extension of patchy dullness through mid and outer zones of each lung. (D) Portable film 22/5/44. Extreme cardiac enlargement. P.A.I., 10·0 cm. Scattered patchy consolidation through both lung fields.

It is suggested that the progressive enlargement of the heart, with increasing dilatation of the pulmonary arc (P.A.I., rising from 8·4 to 10·0 cm. in 4 months) and the scattered consolidation—advancing here and subsiding there—make up a radiological sequence on which the diagnosis of an infected ductus and pulmonary artery may be made with confidence. For autopsy control, *see Fig. 9.*

remarkably, and there is no doubt that the majority have been restored to perfect health, though admittedly the progress of a small number has only been observed for a period of months. Tubbs' (1944) first patient is alive and well 4½ years after operation.

Fatal Cases. Success did not attend our efforts in Cases 1 and 14. In both patients the infection had run a prolonged course and both were in bad condition when surgery was undertaken. The administration of sulphonamides and penicillin before operation was a waste of valuable time. Complete cure has been brought about by surgery alone (Touroff, 1943, Tubbs, 1944): sulphonamides are unnecessary.

The two other fatal cases remain to be discussed. Case 2, a boy of 5, died from hæmorrhage after a second attempt to ligate the ductus. The first ligation performed in October 1940 was followed by a recanalization of the channel with a return of signs and symptoms after temporary improvement. Fig. 11 depicts the course of the blood pressure findings. Shapiro and Keys

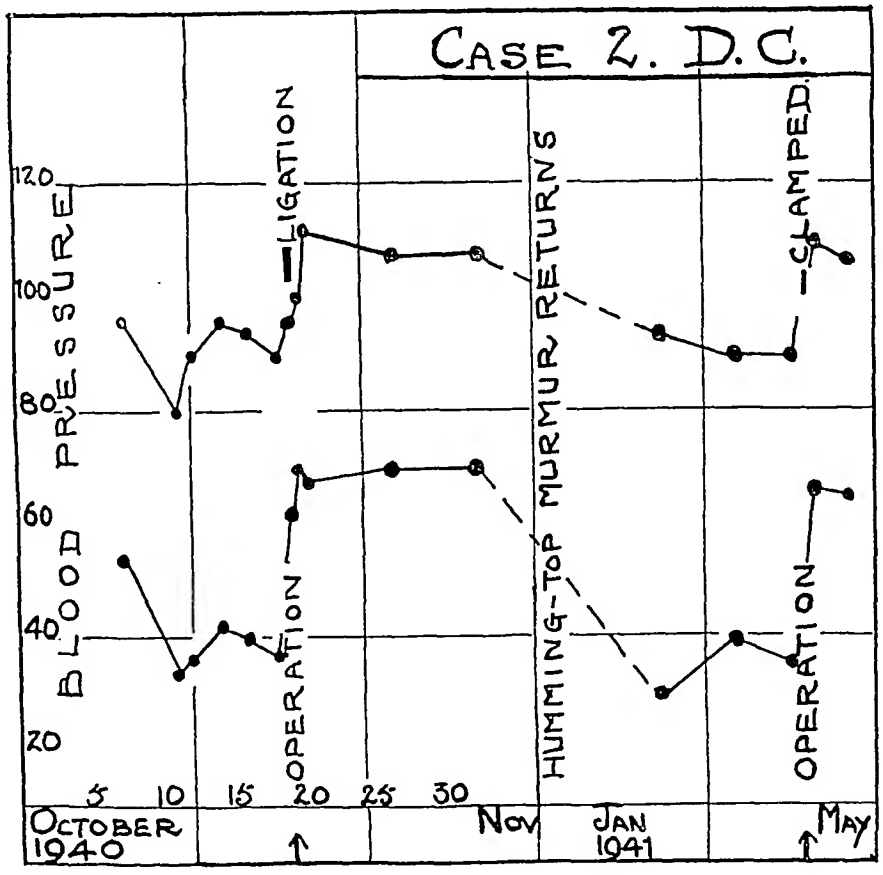


FIG. 11.—Course of the blood pressure in Case 2, a boy aged 4½. The ductus was ligated on 19/10/40. The channel recanalized, the physical signs returned, and the diastolic pressure fell. A second ligation was done on 26/4/41.

(1943) collected the results of 107 ligations report rupture of the ductus at operation in 6. Bleeding can be profuse and exsanguinating and death has occurred on the table. The ductus often belies its appearance. Dilated, friable, and adherent in its postero-medial aspects, it is best regarded as a very fragile structure, tearing readily. Its dissection demands the greatest patience and forbearance, but Touroff's (1942*b*) new technique of sub-adventitial dissection on the under surface of the aortic arch should reduce greatly the operative dangers, facilitate ligation, and shorten the surgical procedure as a whole.

In Case 12 the fatal issue was attributed, in the absence of an autopsy, to a deep-seated mediastinal infection. This child's death, one month after a successful ligation, was a great discouragement and casts a shadow over the whole series. It may be that the necessary

disturbance of the glands and lymphatics at the root of the lung opened a pathway of infection leading from the pulmonary airways to the mediastinal tissues. As a routine procedure dusting with sterile sulphathiazole before closure of the mediastinal pleura might reduce the risk of infection at this site.

Progress of Survivors. The remaining cases—10 in number—have done reasonably well. Progress may be assessed in various ways, of which not the least important is the general clinical impression based on the patient's physical state, sense of well-being, freedom from symptoms, and capacity for exercise, supplemented in the case of a child by the opinion of the mother, or of the patient himself. With such a background a general clinical assessment has been made for each patient. The result after operation in the 10 survivors may be classified as follows.

(1) Excellent: Case 5 (24 months).
(2) Good: Cases 3 (45 months), 8 (7 months), 9 (7 months), 10 (6 months), 13 (6 months).
(3) Fair: Cases 4 (36 months), 7 (7 months), 11 (6 months).
(4) Poor—i.s.q.: Case 6 (9 months).

The times in brackets indicate the period since operation, during which it has been possible to assess each patient's progress. A conservative attitude has been adopted, in that in the case of the children sufficient interval has not elapsed to allow of full correction of their debilitated or subnutritional state, with the result that the present review tends perhaps to minimize the benefits, which ought to become more obvious with the passage of time.

Various measurements, such as height and weight in the case of children, and records of heart size (including measurements of the pulmonary arc) and comparative readings of diastolic blood pressure, are of value in assessing progress. In this connection by far the most spectacular result has been obtained in Case 5, a boy aged 13, whose ductus was ligated on 28/7/42. In the succeeding two years this debilitated youth has improved out of all recognition, having gained 43 lb. in weight and 8 inches in height. Liable to occasional œdema of the feet and ankles before operation, this boy has been fully restored to perfect health. As a measure of physical fitness, he covered 7 miles in an hour on foot in July 1944.

The change in the size of his heart is illustrated by the successive radiograms reproduced in Fig. 12. While the heart size in relation to the thorax is distinctly less in the last X-ray of the series, yet the cardiac area is actually a trifle larger. Successive transverse diameters of the heart amount to 112, 114, and 114 mm. The corresponding transverse diameters of the thorax measure respectively 225, 248, and 256 mm. It would therefore appear that in the rapidly growing child the heart size remains stationary while the body grows until ultimately each becomes adapted to the other. As a rough and ready record of the degree of distension of the pulmonary artery, Evans (1943) has employed a measurement of the distance between the junction of the superior vena cava with the right auricle and the summit of the pulmonary arc, as demonstrated in the frontal view of the chest. For comparative purposes in the one subject this measurement, known as the pulmonary artery index (P.A.I.), is a useful guide to variations in the size of the vessel. It is interesting to have proof of the shrinkage of the pulmonary arc in the successive X-rays of this patient, the pulmonary index falling from 73 mm. before ligation of the ductus to 59 mm. 2 years later, and this despite a considerable growth of the chest with but little corresponding gain in heart size. Along with the decreased distension of the main trunk of the pulmonary artery, the final teleradiogram reveals a great reduction in the vascularity of the lungs. Fig. 13 depicts the effect of ligation on this patient's blood pressure. No one could fail to be impressed with the phenomenal progress which this boy has made. Surgery has brought a cardiac cripple to full working capacity and endowed him with a new freedom.

Less spectacular results have been obtained in the second group, whose progress may be classified as "good." Case 3 had a surgical ligation done on 23/1/41. His immediate progress was retarded by a massive collapse of the left lung and a copious blood-stained

A B C

FIG. 12.—The effect of ductal ligation on heart size. Case 5. (A) Teleradiogram 15/6/42, age 13. Slight cardiac enlargement, dilated pulmonary vessels; m.t.d. 11·2 and P.A.I. 7·3 cm. Cardiac area 106·0 sq. cm. (B) Teleradiogram 13/12/43. The same patient 17 months after surgical ligation. The boy's growth is indicated by the increased size of the thorax, the transverse diameter of which is 24·8 cm. as compared with 22·5 cm. in the previous film. There is a notable decrease in the vascularity of the lungs and the pulmonary arc is smaller, the P.A.I. being 6·8 cm.; in relation to the size of the thorax the heart is smaller, though its actual measurements are very similar. Cardiac area 103·5 sq. cm. (C) Teleradiogram 19/7/44, from same boy, now aged 15 years, 24 months after surgical ligation. Growth has continued. The transverse diameter of the chest is 25·6 cm. The transverse diameter of the heart is as before. The pulmonary artery has continued to shrink, the P.A.I. being now 5·9 cm. The lung fields are clearer. Cardiac area 113·7 sq. cm.
(The heart areas in sq. cm. in these three X-rays have been calculated from the figures of Ungerleider and Gubner, 1942.)

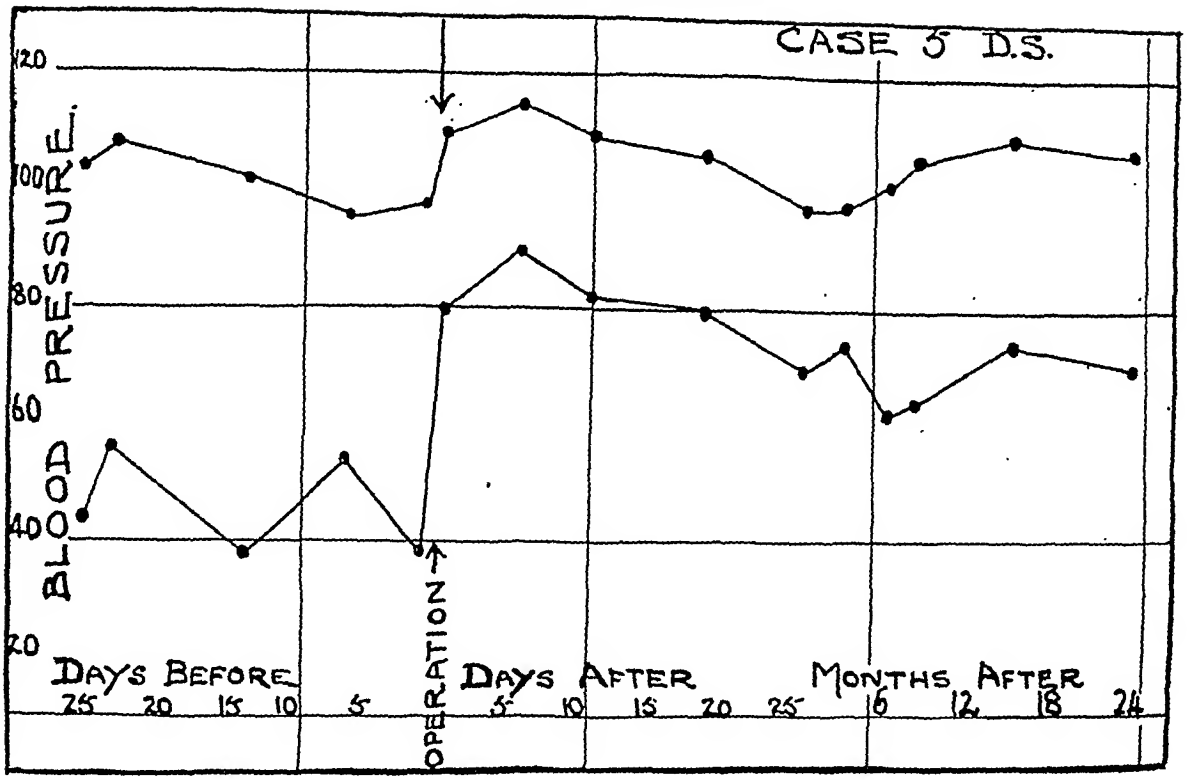


FIG. 13.—Response of the blood pressure to surgical ligation in Case 5. Two years after operation the diastolic pressure is maintained around 70 mm. as compared with a minimum of 38 mm. before ligation. Teleradiograms of this boy's heart are reproduced in Fig. 12.

pleural effusion, from the effects of which he only slowly made substantial headway. Considerable pleural thickening and minor degree of pulmonary fibrosis persist with diminished thoracic expansion. In spite of this he is remarkably well and able for strenuous exercise.

Of the children, Case 10 may be selected. Although a trifle in excess of the standard weight, this boy presented well-marked physical signs and a minor degree of incapacity. Surgical ligation caused little disturbance. He had no post-operative complications and four months later the transverse diameter of his heart had decreased by 1·6 cm. and his pulmonary index by 0·5 cm.

In three patients the response has been assessed as "fair", i.e. a minor degree of improvement, less than anticipated. Case 4, a medical student, had the ductus incompletely occluded by a silver ring. In spite of persistence of the Gibson murmur in a modified form, the transverse cardiac diameter has decreased from 151 to 143 mm. and he expresses himself as convinced of the benefit which he has obtained. Case 7 so far (7 months) shows little improvement for though the diastolic blood pressure is reasonably well maintained (see Fig. 14), X-ray examination suggests that the ductus is not completely occluded. The Gibson murmur returned on the sixth day after operation and persists, though fainter than formerly. This child has not gained weight. Similarly, Case 11—a neglected slum child—though the physical defect has been completely corrected, has not after six months improved in a nutritional sense.

The result has been classified as "poor" in one patient—Case 6. This boy has obtained no benefit though he continues to gain weight slowly. His physical signs returned on the third day after operation. From the appearances of his heart, the vascularity of his lung, and the fall in his diastolic blood pressure, now as low or lower than before operation, it can only be concluded that the ligatures slipped and his ductus is now as widely patent as before operation (Fig. 15). An analysis of the results obtained up to date is incorporated in Table V.

TABLE V

THE EFFECT OF SURGICAL OCCLUSION OF THE DUCTUS ON CERTAIN BODILY MEASUREMENTS

Case No., sex, and Age	Occupation	Time in relation to ligation	Physical capacity	Heart size		Blood pressure		Pleural effusion after operation	Diaphragmatic paresis after operation	Result	Remarks
				m.t.d.	P.A.I.	Syst.	Diast.				
2. m. 4¼	Schoolboy	Before ..	2	96	?	80	34				
		3 mth. after	1	90	?	108	70	Yes	No	Good	Ductus re-canalized later.
5		Before ..	2	90	?	94	30				
		7 days after	—	—	—	110	66	Yes	No	Death	Died from hæmorrhage.
3. m. 18	Clerk	Before ..	3	150	85	150	50				
		3¾ yr. after	1	135	85	124	84	Yes	No	Good	Murmur returned temporarily.
4. m. 21	Medical student	Before ..	2	151	93	130	52				
		3 yr. after	2	143	93	120	56	Yes	No	Fair	Incomplete occlusion by silver ring.
5. m. 13	Schoolboy	Before ..	4	112	73	98	38				
		2 yr. after	1	114	59	108	70	Yes	No	Excellent	Perfect health. Gain of 43 lb. in weight.
6. m. 13	Schoolboy	Before ..	2	132	71	90	48				
		7 mth. after	2	132	72	88	46	No	Yes	Poor	General health i.s.q. Ductus reopened.
7. f. 5	Schoolgirl	Before ..	2	87	52	86	44				
		6 mth. after	2	88	54	102	62	Yes	Yes	Fair	Murmur returned but blood pressure maintained.
8. f. 7	Schoolgirl	Before ..	2	88	52	82	52				
		4 mth. after	1	97*	54	100	74	No	Yes	Good	Health improving steadily
9. m. 18	Shipwright	Before ..	2	130	80	110	60				
		3 mth. after	1	137*	75	135	90	Yes	Yes	Good	Very well.
10. m. 6	Schoolboy	Before ..	2	112	60	102	46				
		4 mth. after	1	96	55	100	70	No	No	Good	Very well.
11. f. 8	Schoolgirl	Before ..	2	96	55	94	34				
		3 mth. after	2	97*	49	108	75	No	Yes	Fair	Slow improvement.
12. f. 10	Schoolgirl	Before ..	2	104	54	126	62				
		1 mth. after	—	—	—	120	80	Yes	No	Death	Died; ? mediastinitis.
13. f. 8	Schoolgirl	Before ..	2	117	64	82	46				
		4 mth. after	1	111	66	125	75	Yes	No	Good	Improving steadily.
						Two Cases of Subacute Bacterial Endarteritis					
1. m. 19	Van driver	Before ..	6	172	105	110	42				
		3 days after	—	—	—	120	65	No	No	Death	Pulmonary collapse.
14. f. 28	Housewife	Before ..	6	152	94	145	42				
		3 days after	—	—	—	115	75	Yes	No	Death	Pulmonary collapse.

Physical capacity has been assessed for each patient before and after operation according to the same scale as in Table IV (see p. 16).

The age given for each patient is that at the time of operation.

Heart size is recorded as maximum transverse diameter (m.t.d.) in mm. in the frontal view. The pulmonary artery index (P.A.I.) is employed as a rough measure in mm. of the size of the pulmonary artery (Evans, 1943).

The minimum blood pressure reading in the period before operation is recorded for each patient to compare with the level at which the blood pressure eventually becomes stabilized after operation.

The occurrence of a pleural effusion or a left-sided diaphragmatic paresis is recorded for each patient in the period after operation.

The clinical assessment of the patient's response to surgery is inserted under "Result."

* A slight tilt imparted to the heart by the elevation of the left dome of the diaphragm makes comparative measurements of the transverse cardiac diameter difficult.

Summary. To summarize these findings, observation of the 14 patients in the period after operation has shown distinct improvement in the general health and physical capacity in 6 (Cases 3, 5, 8, 9, 10, and 13). It is natural that the degree of improvement should be more obvious in the older patients as their physical handicap was greater than that of the younger members of the group. It is satisfactory that these six patients have been restored to normal health and full activity. Cases 4, 6, 7, and 11 have obtained less benefit than anticipated, chiefly for the reason that only partial obliteration of the ductus was obtained in three of them. Two patients, submitted to operation on account of bacterial endarteritis, died shortly afterwards. Two non-infected cases died.

PROBLEMS OF THE POST-OPERATIVE PERIOD

The patient in this period requires constant care and attention. Most have been nursed for 24 to 48 hours in the oxygen tent with considerable benefit. There are features after the

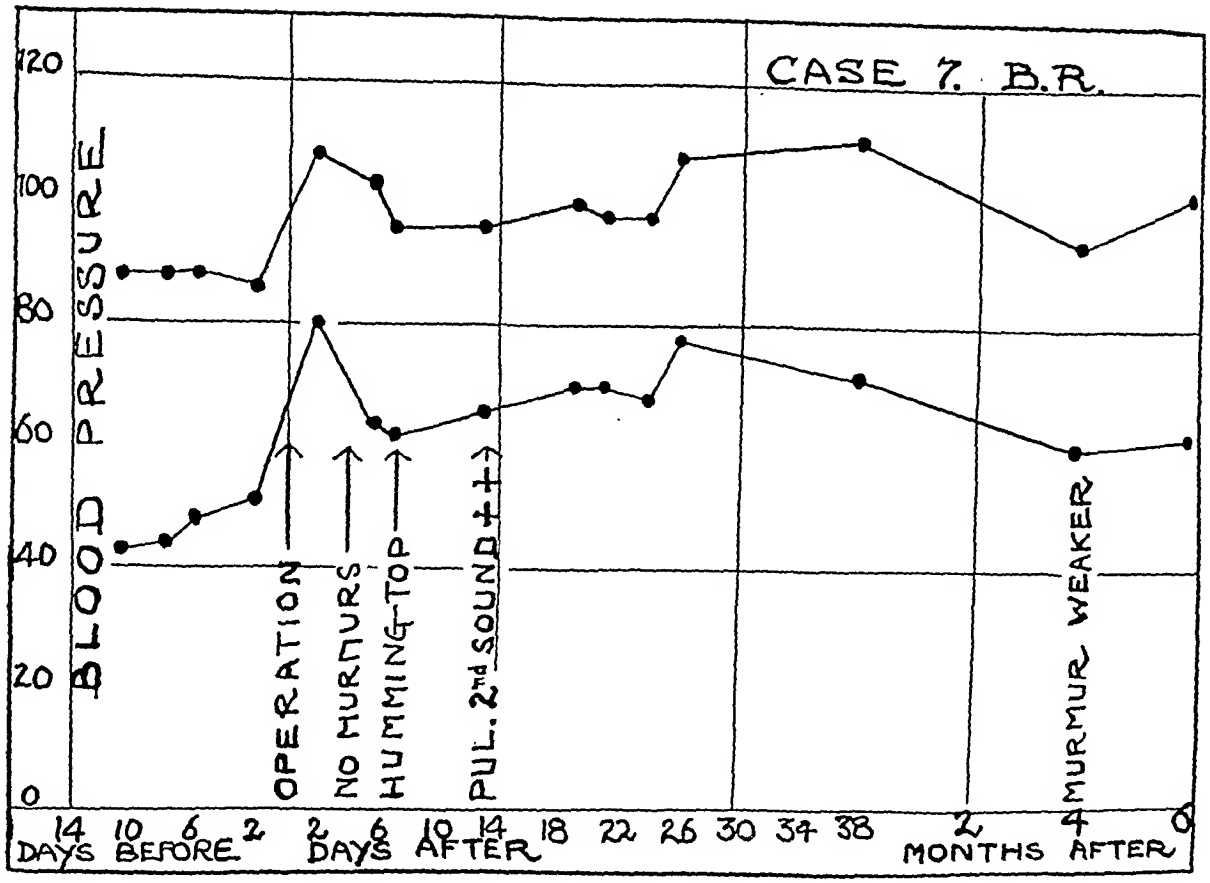


FIG. 14.—Blood pressure response in Case 7. The Gibson murmur returned on the sixth day after operation. Radiological evidence confirmed the re-establishment of the fistula. In spite of this the diastolic pressure is more satisfactory than previously and four months after operation the ductal murmur is weaker than before.

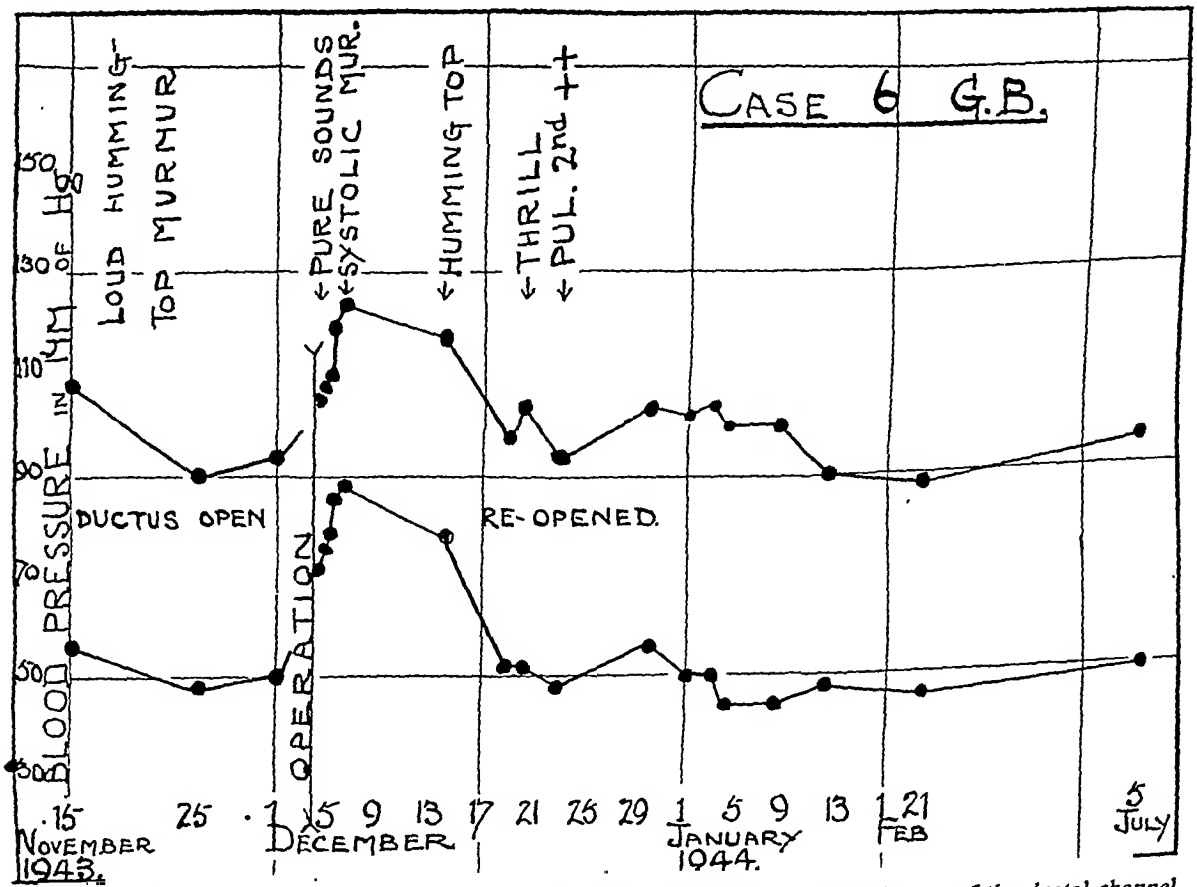


FIG. 15.—Blood pressure response in Case 6. The first indication of re-establishment of the ductal channel was a systolic murmur observed on the third day after operation. The Gibson murmur was recognized on the eleventh day. A week later the blood pressure had fallen and physical signs were then fully developed.

operation that are confusing and difficult to interpret, particularly in relation to the state of the lungs.

Respiratory Complications. Physical signs in the chest are notoriously difficult to interpret after the pleura has been opened, and in acutely ill patients with cumbersome dressings the examination of the lungs can be very difficult. Radiological control is essential. Considerable experience is required in the interpretation of the films (Cleland and Rackow, 1943). Blood in the form of a large hæmatoma of the chest wall at the site of the operative approach can cast a shadow in the radiogram which may at first simulate a hæmothorax, and later, when resolution is in progress, a minor haziness suggestive of a partial atelectasis. Air and blood in the pleura are common. Familiarity with the radiological appearances after operations in the chest is of enormous help in understanding the respiratory complications of the first ten days. It is questionable whether at the conclusion of the operation re-expansion of the lung by intratracheal positive pressure is the best method, in view of the risk of driving accumulated secretion deeply into the alveoli and thereby favouring local collapse and infection. To avoid the risk of stagnation in the collapsed lung, Jones (1940) recommends the use of repeated positive pressure to re-expand the entire lung for a few seconds every 10 or 15 minutes while the pleura is open. Gross (1944) now employs intra-pleural suction to re-expand the collapsed left lung at the conclusion of the operation.

Experience indicates the desirability of withdrawing pleural fluid from the chest. Blood should not be left in the pleural sac. Lush and Nicholson (1944) in emphasizing the advantages of evacuation of the mass of clot in a clotted hæmothorax as the quickest way of restoring respiratory function and preventing infection, point out that the diagnosis is often confused with consolidation, and is confirmed by repeated failed aspirations. This is an aspect of post-operative care warranting close attention, where repeated frontal and lateral X-rays are of the greatest value in conjunction with the clinical findings. Respiratory exercises, oxygen enriched with CO_2, and stimulant expectorants should be started at the first opportunity in the hope of reducing the liability to massive pulmonary collapse.

Recanalization of the Ductus. It is not uncommon for the Gibson murmur to return. In the series of 107 non-infected cases collected by Shapiro and Keys (1943) a continuous murmur persisted after ligation in 14, which may well be an under-estimate of its frequency. Employing light compression of the ductus with two heavy braided silk ligatures and a cellophane wrap, better results were obtained by Gross (1944) than by simple ligation alone. In only 3 of 28 patients in whom cellophane was employed along with double silk ligatures have minimal leaks persisted since operation. On account of these failures Gross (1944) has introduced a new technique for the complete surgical division of the ductus.

It is reasonable to assume that a return of the Gibson murmur signifies a re-establishment of the fistula between the aorta and the pulmonary artery, but attention must be paid to the remarkable observation of Touroff and Vesell (1940) who found that the loud machinery murmur persisted in one patient after the ductus had been *divided* and the stumps ligated close to the pulmonary artery and aorta respectively. Now that Gross (1944) has introduced and recommended division of the ductus, confirmation of this curious observation should be forthcoming. In two patients Touroff and Vesell (1940) noted in the course of the operation that on occlusion of the ductus there was a diminution of the thrill and murmur, both of which could be abolished when the pulmonary artery was lightly compressed. This suggests that the tension of the wall of the pulmonary artery is a factor in the production of the murmur, but it is difficult to understand how a dilated artery can in itself be responsible for the diastolic element or the continuous quality of the murmur. Peacock (1858) has described a case in which the ductus existed in duplicate. Arising from the aorta, one branch united with the right pulmonary artery, the other with the left. It is possible that under similar circumstances one branch might be ligated, the other persist and produce the murmur.

It is worth recalling that a wide open ductus may fail to produce a murmur (Keys and

Shapiro, 1943). In Case 4 of this series, although the ductus was only partially occluded, the continuous murmur, previously well heard, could not always be recognized during the first 14 days after operation ; a systolic murmur took its place ; later the Gibson murmur returned and has persisted in the three years since operation. Similarly in childhood the murmur develops slowly, the age of 4 being commonly reached before its continuous quality enables it to be recognized with certainty. It is therefore true that patency of the ductus can exist in the absence of the continuous murmur. On the basis of the size of the channel and differences in blood pressure between the two circuits, the absence of the murmur on certain occasions is more readily acceptable than its presence when no fistula does in fact exist. For clinical purposes it is wiser to assume, unless proved otherwise, that a return of the murmur signifies a recanalization of the channel.

In the present series of 15 operations done on 14 patients, the ductus was closed on 12 occasions. In one patient (Case 4) a silver ring produced partial obliteration and in two other patients (Case 1 and Case 2, second operation) satisfactory occlusion was impossible on account of local hæmorrhage. Of the remaining 12 surgical occlusions, the typical continuous murmur of a patent ductus developed in the period after operation in 4 instances (Cases 2, first operation, 3, 6, and 7). The related facts are conveniently grouped in Table VI.

TABLE VI

RETURN OF GIBSON MURMUR AFTER SURGICAL LIGATION

Case No.	Ligature material	Number of days before murmur returned	X-ray appear-ances	Fall in diastolic B.P.	Present state of murmer	Present state of patient	Remarks
2	Heavy catgut	60±	+	40	—	Died	Recanalization of ductus confirmed at second operation.
3	Heavy silk (2)	11	?	20±	Absent	Good	No murmurs now; B.P. maintained.
6	Heavy silk (2)	10	++	40	Persists 9 months	Poor	Health in statu quo.
7	Linen tape	6	++	25	Persists 7 months	Fair	Health fair; B.P. maintained.

When the ductus re-opens the first clinical evidence is the detection of a basal systolic murmur, This was observed in Case 6 as early as the third day after operation. It increased in intensity without appreciable change in the level of the diastolic blood pressure until the eleventh day, when the distant continuous hum was first recognized. Thereafter the blood pressure fell and further local signs developed (Fig. 15). On the other hand the typical murmur returned in Cases 3 and 7 with little or no significant alteration in blood pressure (Fig. 16 and 14). In spite of this the ductus was undoubtedly reconstituted in Case 7, as fully developed radiological signs persisted. In Case 3 the presence of post-operative pulmonary collapse, an effusion, and a certain amount of residual fibrosis, made the state of the pulmonary artery and the ventricular excursion difficult to determine. It is remarkable that since the Gibson murmur has finally disappeared a " hilar dance " is evident on screen examination of this boy's chest.

The return of the murmur suggests either a slipping of the knot as a result of its repeated exposure at each heart beat to the strain of the increased blood pressure, or else it may be that the vascular channel is re-established as a result of pressure erosion by the ligature. It was certainly unexpected to find that a structure which normally obliterates itself within a few months of birth should fail to do so when given the opportunity in later life. The problem of satisfactory occlusion is not yet solved, though Ballance and Edmunds (1891) many years ago enunciated the principles involved in the closure of large arteries. The tension with which the knot is tied must be sufficient to approximate

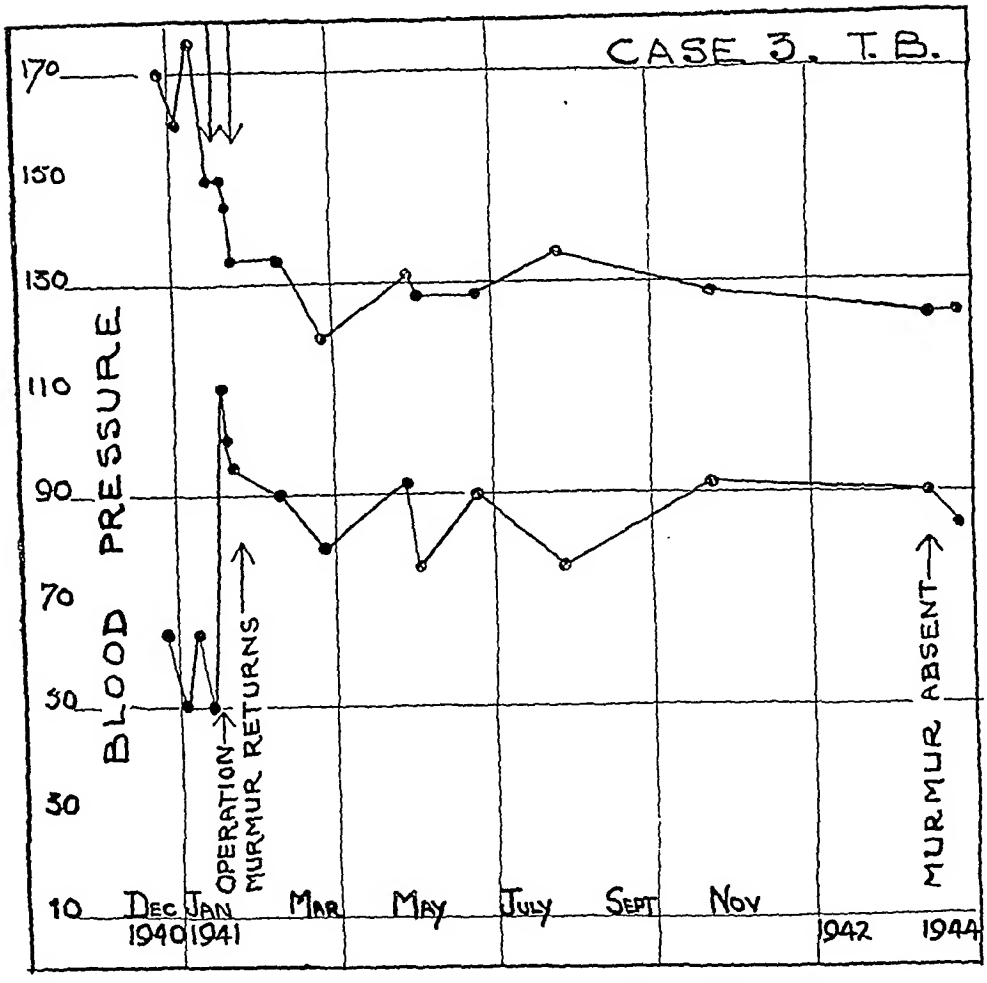


FIG. 16.—Blood pressure response in Case 3. The ductus was ligated in January 1941. The typical murmur returned eleven days after operation and persisted for at least eleven months. When re-examined in February and July 1944 no murmurs could be detected. The blood pressure is well maintained throughout. The effect of ligation on the pulse pressure is striking, the average before operation being 100 mm. and three and a half years after ligation 40 mm.

the intimal surfaces but not great enough to rupture either the inner or middle coats. Similarly, the material employed must be of a size appropriate to the bore of the vessel, the ductus being often as wide as the aorta. Pearse (1940) has successfully applied the observation of Page (1939) on the constrictive effect of cellophane wrapped loosely round the kidney, to the problem of the gradual occlusion of large arteries. Cellophane excites an intense local reaction, causes a steady and progressive constriction at the site of application, and even in 6 or 8 weeks may produce complete obliteration of the lumen of the dog's aorta. The use of cellophane to ensure obliteration of the ductus was suggested by Holman (1940*b*) and has met with considerable success. It can be sterilized by exposure to alcohol or mercury oxycyanide for 12 hours. After the ductus has been ligated with silk in two places and the ends of each knot securely held by clips, a length of cellophane folded into strips about four layers thick is wrapped loosely round the ductus between the ligatures, and its ends tied by catgut (Gross, 1942). Since employing this technique we have not noted a return of the murmur nor any evidence to suggest recanalization. Gebauer (1943) has had failures with this method, as has had Gross (1944), but the results obtained with cellophane are superior to simple ligation and less dangerous than division. The perfect solution to the problem of ligation has not yet been found, but it would appear to consist in a cellular reaction initiated by the application of a reagent locally.

Blood Pressure after Operation. Reference has already been made to the value of blood pressure readings in diagnosis. On closure of the ductus the blood pressure, particularly the diastolic, promptly rises, even above normal. Bourne (1941) has described how in one of his patients a defect in renal function, as measured by the urea clearance test, was evident during this phase: by way of explanation, he suggests that a reflex spastic state of the peripheral and glomerular arterioles accounts for both phenomena.

The maximum blood pressure readings are usually observed within the first two or three days of operation. Thereafter the diastolic pressure falls gradually over a period of a month or more before it becomes finally stabilized, usually about 20 to 30 mm. below the maximum levels recorded in the first few days. In this series the highest diastolic pressure recorded after operation was in Case 9. Before operation his readings were 110/60, on the third day after, 144/112, and three months later 135/90. His blood volume fell from 3360 c.c. per sq. m. to 2830 c.c., the latter being within the normal range for build (Davis, 1942). It is probable that the excess blood volume plays a part in the production of the high blood pressure. We have not made observations on water-balance and renal function after operation. One child (Case 11) had an abrupt rise to 158/94 eight hours after operation, her previous readings having been as low as 94/34.

We have satisfactory figures before and after operation in 10 patients, minimum readings being compared in each instance. On the average the diastolic blood pressure ultimately becomes stabilized at a level 30 mm. higher than before ligation. In 3 patients with incomplete closure in whom local signs of patency persisted (Cases 1, 4, and 7) the average rise in diastolic pressure was 15 mm. The course of the blood pressure response in Case 3 is of interest. Despite the fact that the Gibson murmur returned early and persisted for at least 11 months, there was little disturbance of the blood pressure (Fig. 16). Three years after operation the murmur was absent, without significant alteration in the diastolic pressure. His pulse pressure before operation was 100 mm. and three years later 40 mm. From these facts it is permissible to conclude that with the passage of time local fibrosis initiated by the surgical ligation has finally led to the complete obliteration of the ductus.

The Indications for Surgery

Before recommending surgical treatment the physician must endeavour to weigh the immediate operative hazards against the risks of non-intervention, in the light of the benefits likely to accrue from a successful ligation. This is often a problem of great difficulty, in the solution of which the salient facts gathered from the present series may prove of help.

It is true that a proportion of patients with patency of the ductus live to middle age, and follow active and useful careers, being little the worse for the congenital flaw, but they are in the minority. By the time the age of 40 to 50 is reached the lesion is exceedingly rare. In childhood it is difficult, if not impossible, to select with certainty those patients who in the natural course of events may expect to reach the age of 30. It is highly probable that when the physical signs are gross, the heart enlarged, the pulse pressure greatly increased, and the response to effort even slightly impaired, the child or young adult has a life-span appreciably less than the average. Hence it is probable that those patients who survive to the third or fourth decade have minimal physical signs in early life—a soft murmur, a heart of normal size, and a blood pressure but little disturbed. They are active people, capable of cultivating many interests, but their expectation of life is reduced, though not to the same extent as in the former group that have more pronounced signs and symptoms.

The need for surgery is more obvious in the symptomatic group, particularly if there be evidence to suggest the early onset of congestive heart failure. The justification for recommending a major surgical procedure in the second group, whose signs and symptoms are minimal, is on less secure grounds, and yet there is good reason for believing that surgical ligation can prevent future difficulties and prolong life. Surgery can restore bodily nutrition, correct under-development, abolish circulatory symptoms, prevent the onset of congestive heart failure, and probably forestall the most serious of all complications, subacute bacterial endarteritis. There is, therefore, much to be said in support of the views of Vedoya (1942) and his colleagues who urge that operation should be undertaken as early as possible in every case of patent ductus.

Unfortunately the operative risks are considerable. If surgery was as safe and as certain

in its results as in other disorders of childhood, there would certainly be less hesitation in recommending ligation. Apart from injury to the ductus, exsanguinating hæmorrhage, and a stormy convalescence with the risk of serious respiratory complications, there is also the possibility of a deep-seated infection. There is, however, every reason to assume that as surgical technique improves, as knowledge of the most certain means of ductal obliteration increases, and as experience of appropriate post-operative care of the lungs develops, so in the future a reduction in operative mortality can be confidently anticipated, and a shorter and less tiresome convalescence assured. Of the 107 non-infected cases collected by Shapiro and Keys (1943) there were 9 deaths after operation, more than half the ligations being done by two surgeons—Gross (1944) and Jones (1940). With further experience the mortality rate may be reduced to 5 per cent in non-infected cases.

As pointed out by Gebauer (1943), age is an important factor in the selection of suitable patients for this procedure. It is well known that children tolerate intra-thoracic interference better than adults. Edwards (1939) in a series of 199 cases of bronchiectasis treated by lobectomy had no deaths amongst 38 children between the ages of 4 and 16, whereas during the fourth decade his mortality rate was 30 per cent. The speed with which a child under 10 will rally after ductal ligation is remarkable. Gross (1939) has had children out of bed 24 hours after operation and ambulatory on the third day.

In addition to their tolerance for this operation, there are other good reasons for selecting childhood as the most favourable time for operation. Under the age of 10 years, the ductus is as a rule longer, more readily approached and defined; and the operative field less circumscribed: this facilitates ligation. As age increases, even in the 'teens, the pulmonary artery grows larger, encroaches on and even over-rides the aorta, and with this the ductus tends to be shorter, wider, and perhaps flimsier and more inaccessible: in consequence ligation becomes increasingly difficult. By the age of 20 or 30 atheromatous changes about its orifice with sclerosis of its walls predispose to tearing of the coats when the ligatures are applied. For these reasons younger patients make the better subjects.

This does not imply that at first recognition the non-infected ductus warrants a recommendation for surgery. The physician must be guided by the progress of the patient, who should be under observation from time to time for six months as a minimum. There is always the possibility that the ductus may close spontaneously. If it has not done so by the age of 9 or 10, and the physical signs remain gross, then the risks should be faced in the hope of rendering the future more secure.

To justify operation between the age of 10 and 20, the patient's disability must be more severe than in the younger group. At this time pathological changes begin to make their appearance in the pulmonary artery and with every additional year of age the patient's immediate reaction to the surgical disturbance is likely to be more severe. After 20 there is at present little justification for recommending surgery, as by adapting themselves to their limitations many of these patients will keep reasonably well and sufficiently fit to follow an occupation. Should symptoms become more severe, or congestive heart failure threaten or appear, then after suitable preparation surgical ligation should be recommended. The risks are greater than in younger people, but are justified in that when signs of heart failure appear clinical experience indicates that on medical measures alone this form of congenital heart disease runs a rapid downward course.

It may, therefore, be said that in selecting patients for surgery the main factors to consider are the age and the degree of cardiac embarrassment. In general the younger patient should be accepted for surgery when symptoms are minimal, in the hope that thereby he may grow and develop normally, and be safeguarded from the killing complications that we know may shorten life. In older patients, on account of the operative hazards, surgery can be justified when symptoms, being more severe, warrant the risk. In the presence of an infected ductus surgery is the treatment of choice and it should be undertaken without delay, at any age.

In my opinion surgical ligation of the ductus arteriosus is an outstanding contribution to cardiac therapy. Admittedly the numbers are few, the patients a select group, and the treatment highly specialized and technical, but in no other branch of cardiology are the ultimate results likely to be so perfect. As a technical achievement it is one of the most dramatic and inspiring of operative procedures, demanding the dexterity, courage, forbearance, and resourcefulness that we associate with the highest surgical talents.

Summary

Patency of the ductus arteriosus has been studied in a series of 28 consecutive patients, 14 of whom were submitted to surgical ligation.

In diagnosis emphasis is placed on the almost pathognomonic sign—the continuous murmur of Gibson. In the absence of the characteristic murmur the diagnosis can still be established by the detection of other signs which taken together are of almost equal value. In order of importance these are pulmonary artery dilatation, an increased pulse pressure at rest or after exercise, and a long harsh basal systolic murmur with an accentuated or reduplicated pulmonary second sound.

The defect is in the nature of an arterio-venous fistula. In patent ductus arteriosus the ventricular outputs are unequal, the left exceeding the right by the amount of flow through the ductus. This in turn is regulated, at least in part, by the size of the channel and the degree of resistance offered by the peripheral arterioles of the pulmonary circuit, the constriction of which decreases the burden thrown on the left ventricle by correcting the tendency to an excessive fall in diastolic pressure.

Most cases are observed in childhood and 70 per cent are detected before the age of 20 is reached. After this the condition becomes increasingly rare. The scanty number of adults so affected can be explained on several grounds, such as death in youth, spontaneous closure of the ductus in childhood, or on the failure of the clinician and pathologist to look for this lesion systematically in older patients.

Of 14 patients (Cases 15–28) in whom surgery was judged unnecessary or undesirable, the eldest was 49 and the youngest 5, with an average age of 20 years. Two died, one from intercurrent infection and one from subacute bacterial endarteritis. Slight deterioration in physical capacity was observed in three patients. Two women married and have borne families without undue distress. In one patient, a boy of 6, the ductus closed spontaneously.

Of the 14 patients submitted to surgery distinct improvement in the general health and physical capacity was observed in six. Four obtained less benefit than anticipated, chiefly because complete obliteration of the ductus was not always obtained. Two patients died in the period after operation.

The diagnosis of the infected ductus is discussed. As an aid to its recognition emphasis is placed on the value of repeated X-ray examinations. The radiological appearances are, on occasions, unique: the changing pattern of the heart and lungs makes a sequence so characteristic that the diagnosis of bacterial endarteritis of the ductus and pulmonary artery should seldom be missed.

Two patients submitted to surgery on account of bacterial endarteritis died. Death in each instance was attributed to massive pulmonary collapse.

Problems of the post-operative period are discussed. The occurrence of respiratory complications, recanalization of the ductus after ligation, the significance of a return of the Gibson murmur after operation, and the course of the blood pressure response, are considered.

The selection of patients for surgery demands careful consideration. The main factors to bear in mind are the age of the patient and the degree of cardiac embarrassment. In general the younger patient should be accepted for surgery when symptoms are minimal, in the hope that by ductal occlusion the child may grow and develop normally. In older patients, on

account of the increasing operative hazards, surgery can only be justified when symptoms, being more severe, warrant the risk. In the presence of an infected ductus ligation should be undertaken without delay at any age.

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CARDIAC MANIFESTATIONS IN A CASE OF TUBEROUS SCLEROSIS

BY

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From St. Andrew's Hospital, Northampton

Received October 12, 1944

The case reported in this communication is alive and relatively well at the time of writing. A rhabdomyoma of the heart is strongly suspected, though the diagnosis can be made with certainty only after death.

Case Report

The patient, a young man of 23, was first seen in June, 1942. He was then a high-grade mental defective with a limited vocabulary, though he could give a fairly clear account of his life, and his memory was fairly good. He could read and write, and had a number of interests, such as listening to the wireless, keeping a daily record of the outside temperature, etc. When seen last (June, 1944), he was sprightly, impish, mischievous, and full of tricks, and always highly amused afterwards when taken seriously; he had the outlook of a boy of seven. He was the only child of healthy parents, and there was no mental illness on the paternal or maternal side of the family. Birth and pregnancy were normal, but he was a fretful baby and only began to walk when two years old and to talk at the age of three. He tried school but failed. In 1934 he was incontinent for urine, mostly by day, and passed water very frequently. The patient himself reported that he had attacks of dizziness and falling down, and that he " goes to sleep " for a few minutes sometimes whilst standing, but this was not observed by the parents. He had no epileptic fits while under medical observation for the last two years, but the above-mentioned " turns " might be regarded as epileptic equivalents.

Physical examination showed a youth of asthenic build, 5 ft. 6 in. in height, of poor muscular development, weighing 8 stone 12 pounds. The nose and cheeks were conspicuously covered with sebaceous adenoma in the form of reddish brown nodules of pinhead size, distributed in the classical " butterfly " pattern. The skin of the upper part of the chest had a gooseflesh texture; on the back of the neck were numerous short tags of skin sticking out like bristles, whilst on the back itself there were, especially on its lower part, a few irregular, thickened, whitish-brown areas—plaques chagrinées —and one or two short pendulous polyps. The fundi appeared normal, and no " phakoma " could be detected in the retina. No other congenital malformation could be found by external examination, the skull and the palate were of normal shape, and the testicles completely descended; one observer, however, thought the patient's hands were ape-like. The kidneys could not be felt; a pyelogram was, unfortunately, not practicable. The blood urea was 38 mg. per 100 c.c.; laboratory investigations showed no abnormality in urine, blood, etc. There was no spasticity or paresis, and the reflexes were normal.

The most interesting phenomenon was a total irregularity of the pulse. On palpation it could not be decided with certainty whether this was due to fibrillation or to numerous extrasystoles, though there were periods when three to four beats in quick succession could be felt after each normal beat. It could not be ascertained whether this irregularity had been present for a long time or even since birth, but it was present during the past two years while the patient was under observation. There was no history of rheumatic fever or any other illness that might have affected the heart, and the patient never complained of shortness of breath or palpitation, nor was he cyanosed. The apex beat was in the fifth intercostal space in the

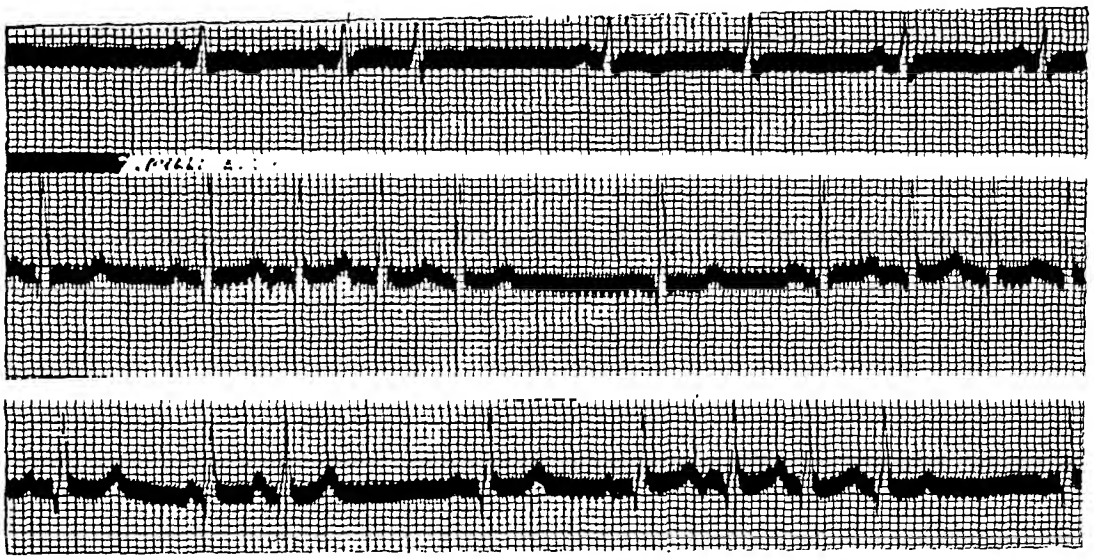

FIG. 1.—Electrocardiogram showing short paroxysms of supra-ventricular extrasystoles and some change of pace-maker shown in lead III.

midclavicular line ; the heart did not appear to be enlarged on percussion, no thrill could be felt, and no murmur was audible, but the action was quite irregular and seemed somewhat faster than at the periphery, presumably because some of the contractions were not powerful enough to reach the radial pulse. The blood pressure was 120/70, the average pulse rate 85. A cardiogram taken on 19/6/1944 (Fig. 1) showed paroxysms of extrasystoles of auricular origin, the latter following each other in such quick succession that their P waves were mostly

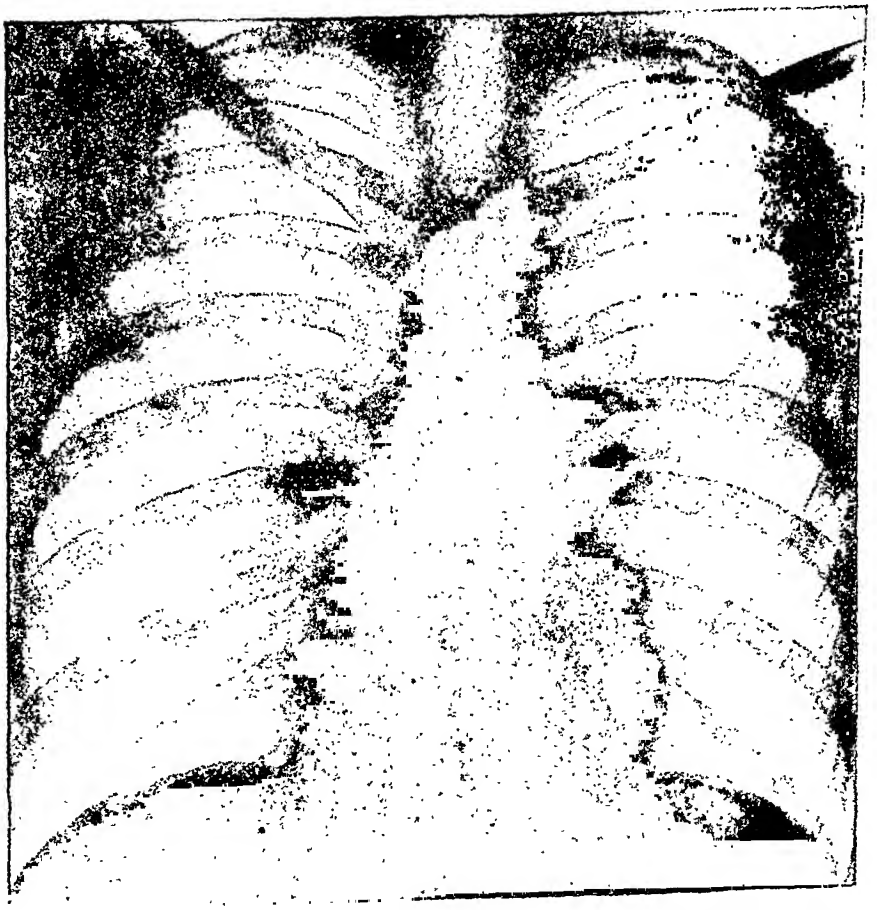

FIG. 2.—Teleradiogram, showing a globular heart with some enlargement to the right.

superimposed on the T waves of the preceeding beats. It appeared that most normal beats were a stimulus for a short chain of extrasystoles. Further evidence of myocardial involvement was the negative and absent T waves in the first lead; the conduction time and the QRS complexes were normal; the S–T segments were hardly displaced; there was no axis deviation. A teleradiogram (Fig. 2) showed a heart of globular shape, the hypertrophy being mainly to the right, with some rounding of the apex; on screening in the left (II) oblique position, the left ventricle appeared closer to the spinal column than normal. This general hypertrophy may account for the balance of the electrical axis in the cardiogram. No evidence of enlargement of the pulmonary conus or arch or of the left auricle was seen on fluoroscopy; the aorta appeared in a normal position. The irregularity of the heart action was clearly seen. Bones and lungs showed no evidence in the X-ray of the osseous and pulmonary manifestations recently described by Ackermann (1944), who gives references to previous findings in these organs. The lungs were clear and the bones did not show cyst formation which has been found in some cases of tuberous sclerosis. These cysts in the bones, together with the skin changes, are a possible link with, von Recklinghausen's disease.

Discussion

Clinical signs of heart involvement due to rhabdomyomata are very unusual. In fact, since the first description of rhabdomyoma by von Recklinghausen in 1862, there seems to exist only one report of a case with an electrocardiogram, taken because of tachycardia and arrhythmia, that was proved at necropsy to be caused by rhabdomyoma. This case, of Wegman and Egbert (1935), a ten months' old girl, the only child of young and healthy parents, had attacks of convulsions with cyanosis and pallor, and a pulse rate of over 200 with an irregular rhythm; periods of varying length of rapid, irregular beats were interrupted by short periods of stoppage or slowing. In the cardiogram reproduced by them, the rhythm is regular, however, and the tachycardia thought to be auricular flutter. There was no enlargement of the heart in the teleradiogram. A diagnosis of a congenital heart lesion was made, the nature of which was not clear. At the post-mortem examination rhabdomyoma nodules were found invading the conducting system, and also situated on the mitral and tricuspid valves. There were numerous small cysts in the kidneys. No evidence of tuberous sclerosis was found in the brain.

In the 51 cases of congenital rhabdomyoma of the heart that have been reported up to date, 29 (57 per cent.) were associated with tuberous sclerosis according to Labate (1939), who gives a tabulated survey of all cases. In 4 cases tuberous sclerosis was not found; in 18 it is not mentioned. Labate's own case was a cyanosed baby that lived only three hours: the heart was very enlarged, and had two large tumours in the interventricular septum, as well as various congenital malformations; tuberous sclerosis of the brain was present, and also a cerebral tumour on the floor of the left lateral ventricle.

No irregularity of the pulse was noted in the cyanosed baby reported by Rae (1938), but no cardiogram was taken; the heart appeared enlarged in the X-ray. At autopsy a large rhabdomyoma was found in the interventricular septum, as well as a patent foramen ovale and patent ductus arteriosus. There was also an enlarged liver and spleen. Rae himself comments that " it is unlikely that the conduction could have remained undisturbed."

Most of the cases reported were newborn babies or infants who lived a very short period. Five cases were over 15 years at the time of death; the oldest, that of Steinbiss (1923), was 35 years of age. Steinbiss reports on six cases that he has seen over a period of ten years; all of them had tuberous sclerosis and rhabdomyoma of the heart at post-mortem examination. He found that up to 1923, 30 cases of rhabdomyoma of the heart had been reported, of which 22 had tuberous sclerosis. Steinbiss sought especially in his cases of tuberous sclerosis for

evidence during life of rhabdomyoma of the heart, but he could not find evidence of this in any of his cases by percussion and auscultation, and there was no alteration in the pulse.

It is indeed astonishing that clinical manifestations of rhabdomyomata have not been found more frequently. Whether the tumour appears as a solitary nodule, which may attain a considerable size, or scattered throughout the myocardium as the multiple type, or in form of diffuse rhabdomyomatosis, one would think that in most cases it would interfere with the spread of excitation within the heart or cause the formation of heterotopic beats. The effect will depend on its position; if the heart action is irregular, the tumour may be expected to lie in the path of the conducting system; sudden or early death may be due to obstruction of a valvular orifice. It is conceivable that large, solitary tumours protruding into a heart chamber might be made visible through contrast visualization after the method of Robb and Steinberg with diodrast.

As it is not uncommon to find ventricular tumours of the brain in tuberous sclerosis, it has to be borne in mind that the cardiac disturbance in our case might have its origin in some hypothalamic lesion.

Summary

A case of tuberous sclerosis with an irregular heart action and cardiac hypertrophy is reported; it is assumed that this may be due to rhabdomyomata.

It seems that there are no published reports with cardiographic and X-ray abnormalities of any cases, suspected during life of having rhabdomyoma.

I wish to thank Dr. T. Tennent, Medical Superintendent, St. Andrew's Hospital, Northampton, for his permission to give an account of the case.

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COR TRILOCULARE BIAURICULARE

AN UNUSUAL ADULT HEART

BY

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Minor degrees of congenital malformation of the heart are fairly commonly discovered at routine post-mortem examinations and are compatible with normal life and age. Major degrees of congenital malformations are rarer and usually incompatible with long life. However, some who have lived to a good age are recorded.

The earliest imperfect descriptions of bilocular hearts are by Pozzi in 1673 and Lanzoni in 1676. The first fully described case is by Wilson in 1798; he lived for seven days. Many cases have since been described, and Peacock (1866) collected ten. Six cases have been described during this century alone, while Maude Abbott (1927) in her series of 850 autopsies collected seven. The highest recorded age is 16 (Rudolf, 1899).

Trilocular hearts are commoner, the bi-auricular being much more common and more favourable to life. The earliest recorded case is by Chemineau (1699). In Abbott's series fifteen cases are recorded, and there are many more individual reports. Peacock (1866) records the oldest age as 24. In Abbott's series, 35 years for bi-auricular and 31 years for bi-ventricular are given as the maximum ages, but Young (1907) records one, aged 39, and Hedinger (1915) one, aged 56 years.

A common arterial trunk or persistent truncus arteriosus in conjunction with the above abnormalities is even rarer. Only 23 cases have been recorded (Abbott, 1927), and the maximum age recorded by Abbott is 12 years. Vierordt (1898) records one at 16 and another at 19 years.

The following is an extract from the General Register of Deaths in England and Wales, where congenital heart disease was certified to be the *primary cause.*

Age group	1940	1941	1942	Age group	1940	1941	1942
35	17	19	12	60	3	3	8
40	11	11	10	65	1	1	2
45	5	9	8	70	1	1	1
50	6	8	8	75	—	1	—
55	2	2	2				

Unfortunately it does not record the type or degree of malformation.

DESCRIPTION OF CASE

Below is a record of a very unusual case of congenital malformation of the heart—unusual in the age and the gross deformity. Although anatomically a bi-auricular trilocular heart, the auricular septum was membranous and incomplete and therefore functioned imperfectly. There was a single artery from the ventricle (common arterial trunk or persistent truncus arteriosus) and the pulmonary artery probably came as a branch from the innominate artery. There had also been two attacks of theumatic fever with no involvement of the heart.

Mrs. K., aged 56, was admitted to hospital on 10/1/44 with the diagnosis of chronic bronchitis and congenital heart disease with failure. She died the following day.

She had always been blue in the face, and her feet always tended to feel cold. As a child she had

been subject to epileptic fits, " going into jerks and losing consciousness," though never having bitten her tongue nor been incontinent. She had been free of these since her marriage.

How active a life she led is not known. It is known she was married in 1918 and was a widow in 1935. She had no children. In 1944 she was not living with any relatives.

She had previously been in hospital in 1918 with a diagnosis of influenza and mitral stenosis, in 1935 and in 1941 with a diagnosis of congenital heart disease and doubtful acute rheumatism on both occasions.

On examination she was breathless at rest. Cyanosis of hands, lips, and face was present. There was marked clubbing of all her fingers.

The cardiac impulse was diffuse with the maximal impulse in the sixth space in the mid-axillary line. The rhythm was regular. The heart sounds were variable. A blowing systolic murmur conducted into the axilla was heard on admission. No murmurs were heard the next day. In the lungs moist rales were heard all over the chest on both sides. There was an unexplained patch of bronchial breathing over the front right second intercostal space, and behind, between the scapulæ. The urine had a specific gravity of 1012 and a trace of albumen.

The physical signs on her previous admission are of interest. The rhythm was always regular. In 1918 a presystolic murmur at the mitral area was recorded; in 1935 no murmurs were recorded; in 1941 the second sound was accentuated at the aortic area, and a systolic murmur was heard at the third left space and later in the fourth left space. The blood pressure was 136/74 in 1941. Cavernous breathing and bronchial breath sounds were heard at the right apex at the front and back of chest.

The blood count was: hæmoglobin 122 per cent, red blood cells 7,500,000, colour index 0·81, and white blood cells 8400. Unfortunately there is no record of any X-ray or cardiographic examination.

Post-Mortem Examination

The body was that of a small-built woman. Height and weight were not recorded. Except the heart all the organs were on the small side. Signs of congestive failure, with marked congestion of lungs, liver, and kidneys, were present. There was some evidence of chronic bronchitis in the lungs, but it was not very much. There was intense atheroma of the aorta. The left kidney was normal. The right kidney was very small but normal macroscopically and without evidence of arteriosclerotic changes: this was the only other developmental abnormality.

The pericardium was normal and contained a little free fluid. The shape of the heart was triangular with the base superior and the apex inferior. The anterior surface was formed by the ventricle, while the auricle was situated above and behind the ventricle, with two auricular appendices lying one above the other, winding round in a clock-wise direction to the front and ending at the root of the aorta (Fig. 1 and 2). There was moderate hypertrophy of the musculature of both the ventricle and auricles. The heart was not weighed in the fresh state but the weight after fixation in formalin was 310 grammes.

The auricle was incompletely divided by a fibrous septum which ended in a crescentic margin, possibly representing the inferior border of the foramen ovale. Of the two parts, that representing the right auricle was about twice as large as that representing the left. A normal tricuspid valve opened from the larger side and a normal mitral valve from the smaller side (Fig. 3). The right auricular appendix and the wall of the right auricle showed more hypertrophy than that of the left. A superior and inferior vena cava opened into the right auricle, and only two pulmonary veins opened into the left auricle.

The single ventricle represented for the most part that of the left, the right ventricle being represented by a small diverticulum on the right side into which the tricuspid valve opened. There was no sign of any interventricular septum. A single large vessel representing the aorta and guarded by a normal three-cusped valve left the ventricle. There was no pulmonary artery. The coronary arteries took origin from the anterior and left posterior sinuses of Valsalva, the orifice of the right being very large; both arteries showed marked arteriosclerosis and took a somewhat tortuous course on the ventricular surface.

The single vessel arising from the ventricle had no branches until it gave off the innominate artery. The right common carotid artery arose at the junction of the aorta and innominate

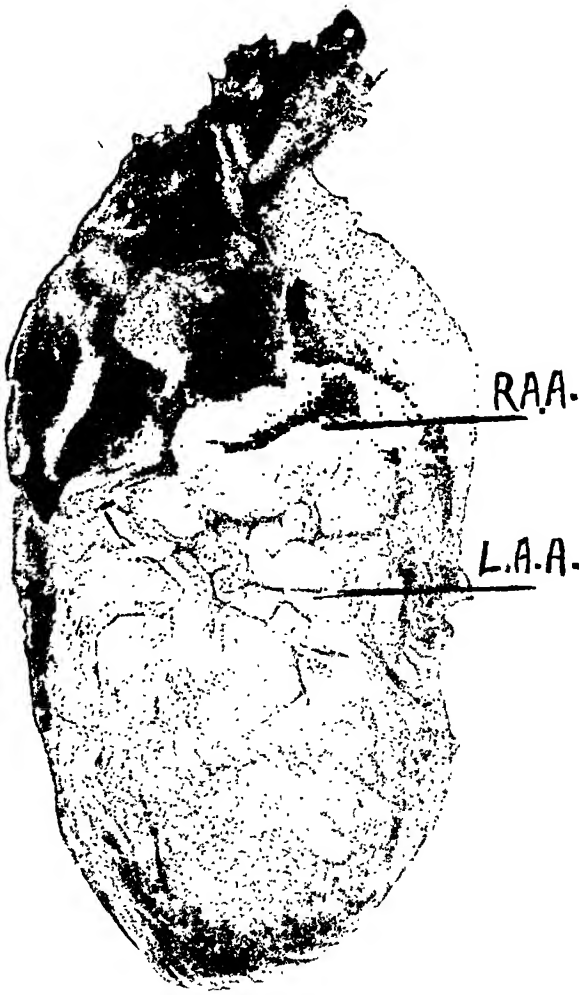

FIG. 1.—Photograph of the heart. R.A.A., right auricular appendage; L.A.A., left auricular appendage.

FIG. 2.—The heart opened. R.C.A. and L.C.A., right and left carotid arteries; L.S.A., left subclavian artery; D.R.V., diverticulum representing the right ventricle; A.P.A., aberrant pulmonary artery; R.S.A., right subclavian artery; I.A., innominate artery.

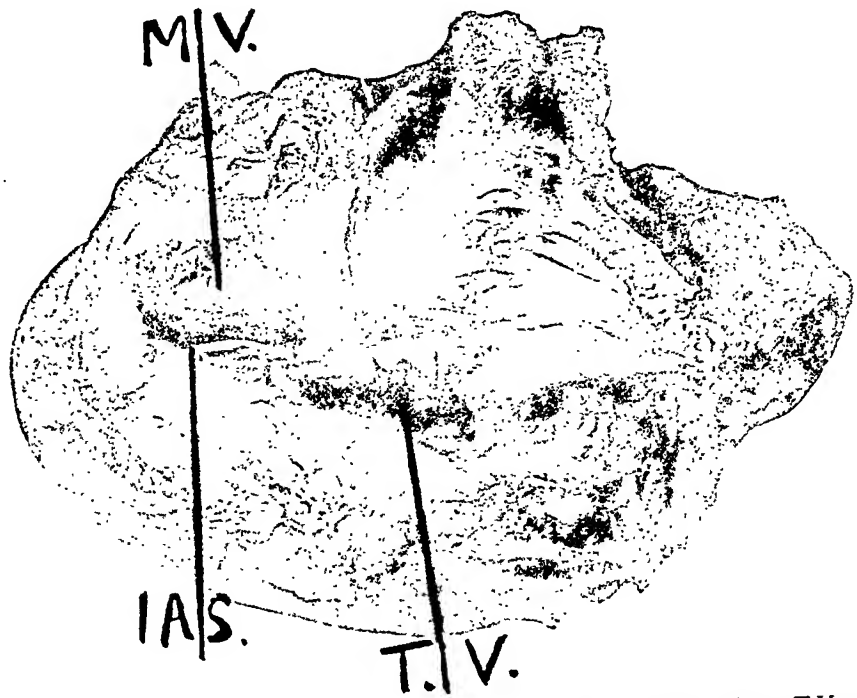

FIG. 3.—Photograph showing the auriculo-ventricular valves. M.V., mitral valve; T.V., tricuspid valve; I.A.S., edge of the incomplete auricular septum.

artery. The left common carotid and left subclavian arteries arose normally from the arch of the aorta. There was marked arteriosclerosis throughout the length of the aorta. The innominate artery divided into two branches, one proceeding outwards being obviously the right subclavian. The other branch appeared to turn downwards and was probably the pulmonary artery, but unfortunately its course was not followed to its termination. The branches from the descending aorta were normal. There was no evidence of rheumatic endocarditis on any of the valves. Section of the ventricular wall showed a patchy fibrosis as the result of arteriosclerosis, but no sign of Aschoff nodes was seen.

Comments

The interest of the case lies in the fact that gross deformity of the heart can occasionally be compatible with normal life to a good middle age.

Such accounts of malformation of individual hearts as are described by Abbott and by Peacock do not show all the features that this heart shows, although each single defect has been described in some heart or other.

This case is the highest age recorded for bilocular and trilocular hearts and for persistent truncus arteriosus.

" When the interventricular septum is defective at its base, as it is in all these cases, there is a tendency for the aortic septum to develop irregularly, thus cutting off a narrow aorta or pulmonary artery, as the case may be, and the calibre of the smaller vessel is likely to become still further reduced in size by the passage of the bulk of the circulation into the larger trunk. For this reason obliteration of one trunk in biloculated hearts, where no interventricular septum is present, is a comparatively common event, and the cases should be sharply distinguished from a true defect of the aortic septum." (Abbott.)

That the single artery in this case was therefore probably not a failure of the aortic septum, but the aorta after separation with loss of the pulmonary artery, is further supported by the fact that there were only three cusps forming the valve. Three or four valves may be present in septal defects of the truncus. The artery arose from the right half of the ventricle. Is it a pulmonary artery turned aorta? A transposition of the vessels or a shift to the right of the vessels is a fairly common finding. Hence probably a true aorta. What about the pulmonary circulation? Unfortunately the pulmonary circulation was never clearly traced post-mortem, but a branch from the innominate artery is presumed to be the pulmonary artery. Various aberrant pulmonary circulations have been described. It is possible that additional blood was supplied to the lungs by the bronchial vessels, but no branch larger than normal was found on the descending aorta. The auricles probably were functionally one although an incomplete septum was present.

A physical sign of note was the area of bronchial breathing over the right chest in the suprascapular region. This observation was made by two independent persons at two different times unknown to each other. No explanation is offered as no post-mortem evidence of any localized lung lesion was found.

Summary

An account has been given of the heart from a woman who lived to be 56 years of age. It was a bi-auricular trilocular heart, but with an imperfect auricular septum. There was a single aorta arising from the ventricle.

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AN UNUSUAL CASE OF A-V NODAL RHYTHM WITH VARYING A-V BLOCK

BY

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In the human electrocardiogram, A-V block prolongs the P–R interval to values exceeding 0·2 sec., while nodal rhythm is characterized by P–R intervals ranging from approximately *plus* 0·12 to *minus* 0·19 sec. (R–P intervals). The simultaneous occurrence of both A-V block and nodal rhythm may produce P–R intervals within normal range (0·12 to 0·2) ; however, this condition can be recognized by the characteristic retrograde P wave pattern (inversion of P II and P III), as recently shown by Langendorf, Simon, and Katz (1944). As the authors point out, this does not exclude the presence of A-V block with P–R intervals between *plus* 0·12 and *minus* 0·19. Since delay or even complete blockage of the A-V nodal impulse may occur on its way to the ventricles (antegrade block) as well as to the auricles (retrograde block) (Lewis, 1914; Lewis, White, and Meakins, 1914; Drury, 1924; and Scherf, 1926), any combination of P–R or R–P interval is compatible with the simultaneous existence of A-V block and nodal rhythm. The relation between P and R depends on the site of impulse formation and the site and the degree of the block.

It is possible that in partial A-V block the site of impulse formation and that of the block are such that the antegrade impulse to the ventricles arrives simultaneously or earlier than the retrograde impulse to the auricles. This has been illustrated by Langendorf *et al.* (1944) in a scheme, but, naturally, this can not be easily demonstrated in actual tracings. The authors present cases with P–R intervals greater than 0·12 sec.

The case presented in this paper is a further contribution to this problem because it illustrates a type of arrhythmia, apparently rare, since we have not seen it reported in recent years.

Case report. The patient, a woman of 81 years, had a history of heart disease for 45 years. With repeated digitalization she had been without complaints for the past three years. She was admitted to hospital on 26/12/43 because of dyspnœa. She had no precordial pain although there was a feeling of precordial oppression. There was no cyanosis, no palpitation, nor œdema. The blood pressure was 160/110. The heart was enlarged to the left; the heart sounds were inaudible, due to dyspnœa and râles throughout both lungs. The patient received oxygen and cedilanid. The leucocytes were 11,400 the following day; her dyspnœa was improved. The pulse rate was 116 on the day of admission, 80 after twelve hours, 60 the next day, and 44 on the evening of the third day, with occasional missed beats. The condition improved during the subsequent three weeks. The temperature ranged from 97·8 to 99·2° during the first fourteen days and between 97 and 98·6° during the following two weeks. A cardiogram was taken on 30/12/43 and another ten days later.

The cardiogram (Fig. 1, a–f) shows intraventricular block of the common type, with pronounced S–T displacement, suspicious of an early, recent myocardial infarct, and a peculiar type of arrhythmia. Only the latter will be discussed in this paper.

The P wave is small and diphasic in lead I and inverted and peaked in leads II and III. This is evidence of A-V block with nodal rhythm if the P–R interval exceeds 0·12 sec. This is true for the first beats in lead I (not shown in Fig. 1) with a P–R interval of 0·20 sec. In the following ten beats (Fig. 1 a), the P–R interval gradually shortens from 0·20 to 0·08, with an R–R interval of about 1·00 sec., so that an inverted Wenckebach phenomenon appears. The next five beats (Fig. 1 b) have about the

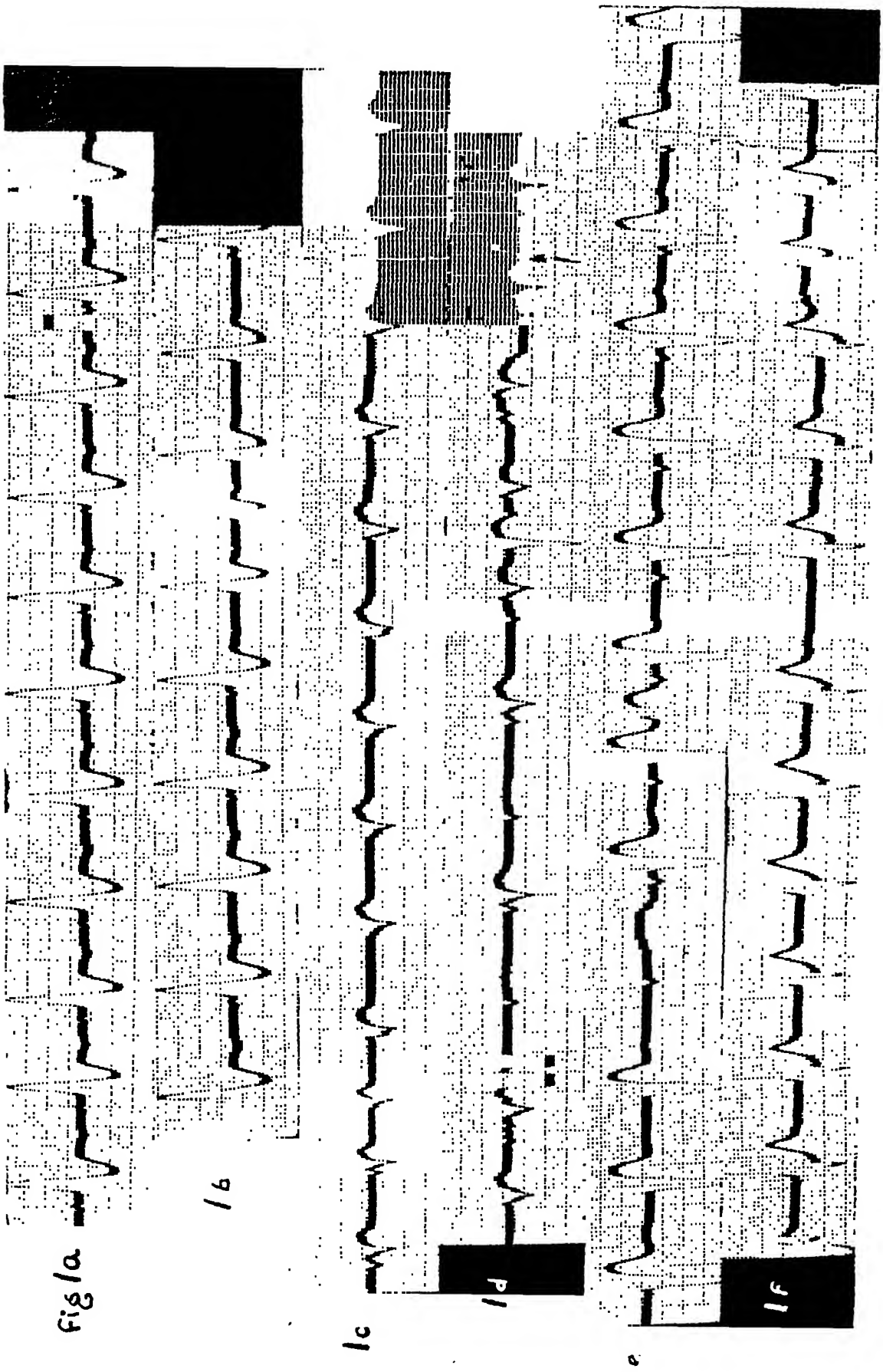

FIG. 1.

same P–R interval of 0·08 to 0·09 sec., followed by four beats without visible P waves (probably fused with QRS). The R–R interval remains about 1·00 sec. The last beat shows a P wave with a P–R interval of 0·12 and a prolongation of the R–R interval to 1·18 sec. Fig. 1 c shows the shortening of P–R intervals in the first four beats of lead II, but more brusquely than in lead I (Fig. 1 a); in beats 3 and 4 the P wave is on the descending limb of QRS with an R–P interval of 0·04 and 0·08 sec. In beats 5 to 7 no P wave can be seen (probably fused with QRS), but the eighth beat is similar to the fourth. It is possible that the P wave blunts the otherwise peaked S wave in beats 9 and 13, which would represent an R–P interval of about 0·1 sec. In beat 15 (beat 1, Fig. 1 d) P is probably on the ascending S limb (R–P=0·14 sec.), and it is immediately after the S wave in the next beat (R–P=0·16 sec.), followed by a short run of 2 : 1 A-V block with increasing P–R intervals from 0·08 to 0·2 before and after the interpolated ventricular beat; in the following six beats (only the first one is shown in Fig. 1 d), the P–R interval is about 0·18 sec. The R–R interval is about 1·00 throughout lead II except the period of 2 : 1 A-V block, where the interval increases to 2·16 and 2·13, exceeding the sum of two normal R–R intervals. In the first three beats of lead III, the P–R interval is 0·20 sec., followed by six beats with narrowing P–R (0·08 sec.), in the following three beats no P wave can be seen. Fig. 1 e starts with the next beat after this episode without a P wave, followed by a blocked P wave. The R–R interval is 2·36 sec., significantly greater than the sum of two usual R–R intervals. The next beat shows a P–R interval of 0·13, the subsequent one of 0·20 (Wenckebach phenomenon). This is again followed by a period of five consecutive beats with shortening of the P–R to 0·05 sec. (inverted Wenckebach); in the last beats no P waves are discernible (fused with QRS).

The first two beats of lead CF_4 have an R–P interval of 0·18 and an R–R interval of about 1·0, followed by a blocked P wave and R–R interval of 2·20, the same phenomenon as in Fig. 1 e in lead III. The next beat has a P–R interval of 0·20, gradually shortening to 0·06 in the consecutive seven beats. The R–R interval is about 0·97. Fig. 1 f starts with the last beat of this episode; the second, fifth, and sixth beat show a notch in the S–T segment, representing the P wave with R–P intervals of 0·12, 0·18, and 0·16, followed by a P–R interval of 0·22 and a prolongation of the R–R interval to 1·38, similar to the episode in Fig. 1 b. The P–R shortens in the following beats to 0·16. In lead CF_5 the first three beats have a P–R interval of 0·20, which shortens to 0·08 in the consecutive five beats; no P wave is discernible in the following beats (fused with QRS). A cardiogram, taken after ten days, reveals only intraventricular block with prolonged P–R interval and regular rhythm.

Discussion

The contour of P waves, small and diphasic in lead I, inverted and peaked in leads II and III, speaks for nodal rhythm. If, according to Langendorf, Simon, and Katz (1944), the P–R intervals exceeding 0·12 sec. are due to the association with A-V block, the variation of the P–R interval, as shown in Fig. 1, could be explained with varying degree of A-V block. This could be regarded as evidence for the view of these authors, that the presence of A-V block in nodal rhythm is possible even when the P–R interval ranges between *plus* 0·12 and *minus* 0·19 sec. The episodes with shortening P–R intervals, until P coincides with or follows the QRS, could be explained with improving orthograde A-V conduction; when P follows QRS, the forward conduction is at an optimum. This phenomenon might be regarded as due to facilitation which brings the conduction time more nearly to normal values. Occasionally, a P wave is blocked, in lead II in two consecutive beats, producing transitory 2 : 1 A-V block (Fig. 1 d), followed by Wenckebach's phenomenon. This explains the temporary lengthening of the R–P intervals after the pauses. In lead I (Fig. 1 b) and lead CF_2 (Fig. 1 f) a beat with a P following QRS is succeeded by a beat with P preceding QRS and a markedly, prolonged R–R interval. Under the assumption of varying forward A-V block this must be explained with an abrupt prolongation of A-V conduction.

There are, however, several difficulties encountered with this interpretation, for instance, the sudden transition from best to poorest conduction, the irrregularity with which the various episodes occur, and the rather broad range of P–R and R–P intervals. Perhaps these difficulties might be better explained on the assumption of nodal rhythm with varying orthograde as well as retrograde block and with a discrepancy in the time course of variations of orthograde and retrograde conduction. If the improvement of forward conduction proceeds with transitory, constant, or deteriorating retrograde conduction, and if the prolongation of forward conduction coincides with an improvement of retrograde conduction,

a rather abrupt increase of the P–R intervals might be produced. The assumption of varying retrograde and orthograde block with discrepancy in the time course of variations might also better explain the broad range of P–R variations from *plus* 0·22 to *minus* 0·19 sec. The assumption of different phases of conduction disturbance in forward and retrograde A-V block in different parts of the A-V node appears to be compatible with the demonstration of different degrees of retrograde and forward A-V block (Langendorf and Katz, 1942).

Another possible explanation is the assumption of two nodal pacemakers discharging at about the same rate, but the upper one coming progressively later. If it comes late enough, it discharges the lower pacemaker, causing the latter to discharge at a later time. This would explain the R–R prolongation at the end of lead I (Fig. 1 b) and in lead CF_2 (Fig. 1 f). When the longer pauses occur, it is assumed that the upper pacemaker discharges the lower twice in succession and is itself blocked from the ventricles. The lengthening of the R–R intervals after these pauses is assumed to be due to a third discharge of the second pacemaker. A very similar mechanism has been described as interference phenomenon of a ventricular pacemaker and the sinus node. In this interpretation P represents the upper pacemaker with retrograde conduction, QRS–T represents the lower pacemaker with orthograde conduction. We are inclined to favour the first interpretation. The disturbance is probably on a neurogenic basis.

Summary

A case is presented with P–R intervals varying from *plus* 0·22 to *minus* 0·19 sec. The type of P waves is nodal. Episodes of gradual shortening P–R intervals, until P follows QRS, of blocked P waves followed by Wenckebach's phenomenon, and abrupt transition from R–P to P–R intervals were observed. Two alternative interpretations are offered: (1) assumption of nodal rhythm with varying degree of at least forward, and possibly of both forward and retrograde conduction, or (2) assumption of two nodal pacemakers.

We wish to thank Dr. L. N. Katz, Michael Reese Hospital, Chicago, for his interest and his valuable suggestions in the preparation of this paper.

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PERICARDITIS AND COMPLETE HEART BLOCK DURING THIOURACIL THERAPY

BY

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From the Harrogate General Hospital

Received October 12, 1944

Thiouracil has been used with success in many cases of thyrotoxicosis (Himsworth, 1944). Reported complications include agranulocytosis, rashes, and fever (Astwood, 1943). In the following case the drug had to be stopped on account of a severe cardiac reaction.

Case History

Mrs. G. W. was first admitted to hospital in 1932 at the age of 21 with a diagnosis of thyrotoxicosis. Both lobes of the thyroid were uniformly enlarged, and a fortnight after admission the right lobe and the isthmus were removed. During convalescence she developed nasal catarrh with fever, and Mr. Pavey-Smith reported that both tonsils were infected. At the same time the histological report on the excised portion of the gland revealed a simple colloid goitre. Nevertheless, a month later the left lobe was removed and the tonsils were left in situ. Following this she kept in good health until 1942, when she began to suffer from a recurrence of tonsillitis and from symptoms of thyrotoxicosis. In February 1944 she was seen by Mr. Pavey-Smith at Ripon Hospital, who found the tonsils to be flat and red, with some pus in the crypts. In view of the symptoms of thyrotoxicosis he advised admission to Harrogate for investigation. Unfortunately this took place during his absence owing to illness, and his house surgeon, unable to find the evidence of tonsillar sepsis, referred her to the surgeon, who thought that a further thyroidectomy might be needed, but desired first to know if she might be a suitable case for thiouracil.

On examination she was flushed and anxious with a fine tremor. There was slight exophthalmos. The heart was not enlarged and there were no murmurs. The basal metabolic rate was +27. The blood sedimentation rate was normal. She had never suffered from rheumatism.

Thiouracil was started on April 14 in doses of 0·2 g., five times daily.

Further estimations of the white cells and of the basal metabolic rate were made as shown below.

Date	Basal metallic rate	Leucocytes per cub. mm.	Polymorphs per cub. mm.
11/4/44	+ 27	11,000	6,000
17/4/44	+ 24	9,000	5,500
20/4/44	—	9,000	4,500
21/4/44	+ 22	12,000	8,000
26/4/44	—	13,000	9,500
29/4/44	—	27,000	22,000

On April 21 she complained of a tight feeling across the front of her chest: otherwise she felt much better. Screen examination on April 24 showed that the transverse cardiac diameter was not increased although there was a slight fullness in the pulmonary area.

On April 25 her temperature was 100° F. There were no physical signs and it was decided

to continue thiouracil since she had had a similar spike before the drug was started. On the following day the temperature was 101° F.; the next day it was 102° F., and she now complained of rheumatic pains in the legs. At 4.30 a.m. on April 28 she was seized with a severe pain in her chest which radiated up to the neck and to both shoulders. The pain was worse on inspiration. Thiouracil was stopped. When examined at 10.0 a.m. she was sitting propped up and was in considerable pain. The heart sounds were sharp and the rate was slower than would be expected with a temperature of 100° F. Morphia, 1/4 of a grain, was given and a cardiogram was taken (Fig. 1).

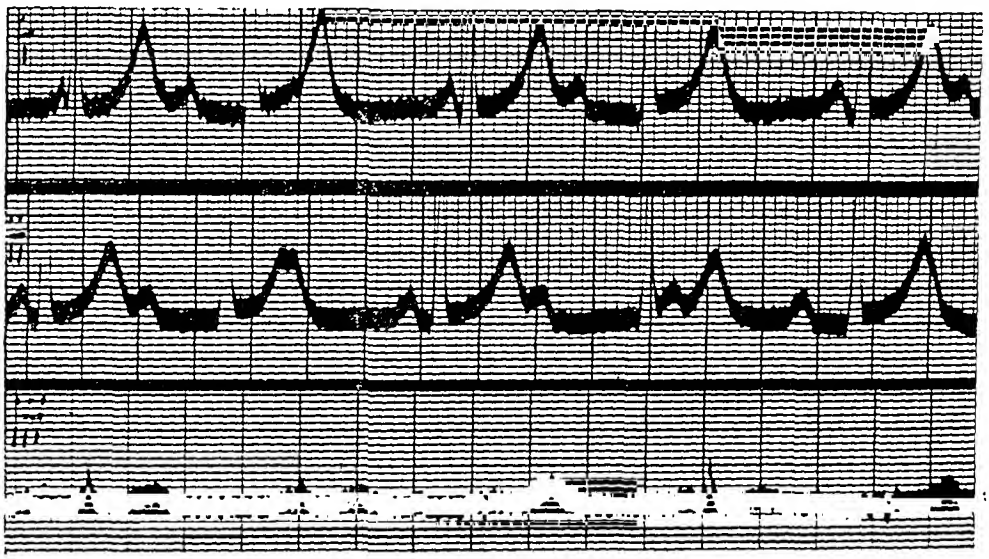

FIG. 1 (28/4/44).—Complete A-V dissociation. Auricular rate, 130; ventricular rate, 84. (*Reduced to 4/5ths.*)

On May 1 a widespread pericardial friction sound was audible. Slight jaundice was present (the Van den Berg showing a weak immediate positive reaction with 0·8 units of bilirubin), but the liver was not enlarged nor tender. All her pains were much improved. By May 4 pericardial friction was much less obvious, and on May 11 traces only were audible at the base of the heart.

The first cardiogram (28/4/44) (Fig. 1) shows complete A-V dissociation with an auricular rate of 130 and a ventricular rate of 84. In Fig. 2 (29/4/44) there is elevation of the S–T

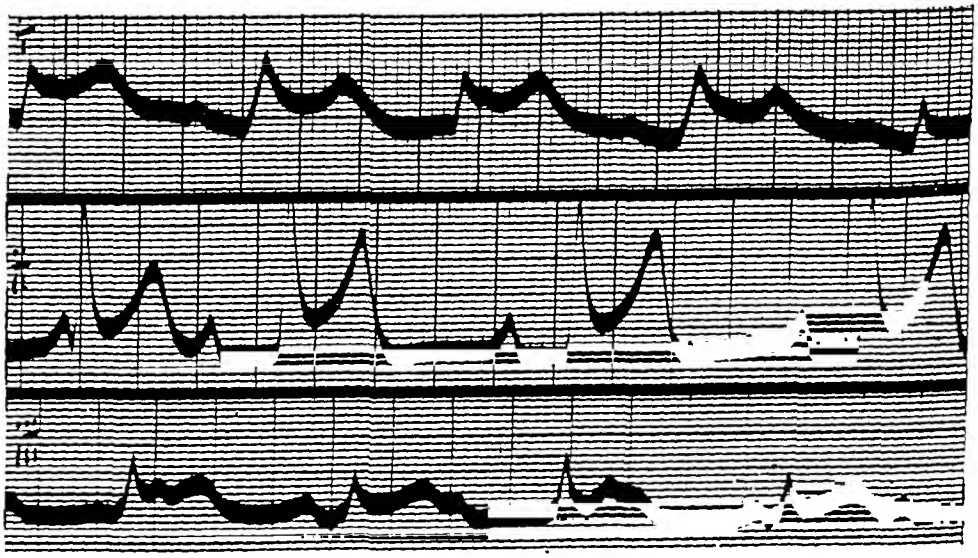

FIG. 2 (29/4/44).—Elevation of S–T junction in all leads. Complete dissociation present in leads I and II. Dissociation changes to 2 : 1 heart block in latter part of lead II. (Reduced to 4/5ths.)

segment in all leads. Complete dissociation persists in leads I and III, but in lead II the dissociation gives place to 2 : 1 heart block in the latter half of the tracing. In Fig. 3 (1/5/44) latent heart block is present with a P–R interval of 0·23 sec., and T is inverted in all leads, still with a raised S–T segment in lead II. Subsequent cardiograms show a gradual return to normal.

Subsequent course. The patient was re-examined in November and in January 1945. There was only a soft apical systolic murmur between the heart sounds. The cardiac silhouette presented the same appearance as in April. She is now back at work.

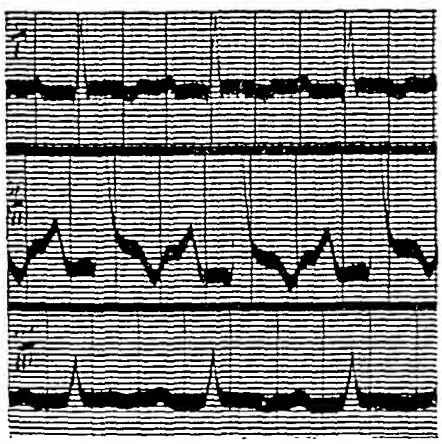

FIG. 3 (1/5/44).—Latent heart block (P–R, 0·23 sec.).—Inversion of T in all leads with high take-off from R in lead II. (Reduced to 2/3rds.)

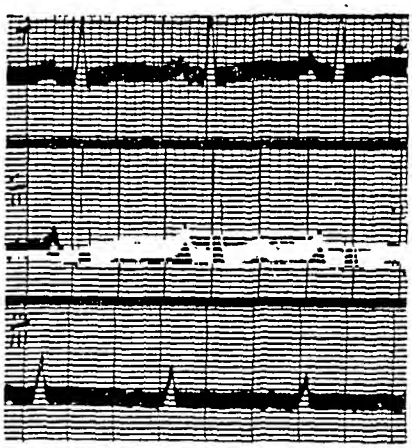

FIG. 4 (11/5/44).—Flattened T waves, otherwise normal. (Reduced to 2/3rds.)

DISCUSSION

It will be conceded this case was hardly suitable for thiouracil therapy. Had the notes of the previous admission or the recent report of the ear, nose, and throat surgeon been available, the drug would not have been given. But no cardiovascular complications have yet been recorded from thiouracil. Fever may occur from the eighth to tenth day and it does not seem by itself to be dangerous (Johnston, 1944).

Although the patient was 33 years of age and had never previously suffered from rheumatism, the attack resembled most an acute rheumatic carditis. On the third day of fever she had pain in the limbs, and next morning she had severe pain in the chest. With the onset of the precordial pain the pulse rate fell from 120 to 90 and complete A-V block was recorded a few hours later. On the following day the cardiogram showed changes suggestive of pericarditis and widespread friction became audible soon after. On the other hand, at no time was there an acute tonsillitis nor did she complain of a sore throat. Salicylates were not given, yet the fever subsided on the day that thiouracil was stopped, and her pain went two days later. It seemed as if the attack was caused in some way by thiouracil. No valvular lesion developed during the succeeding eight months.

It would appear as if caution should be exercised in administering thiouracil in the presence of a septic focus.

SUMMARY

A case of pericarditis with complete heart block is described in a patient receiving methyl thiouracil for thyrotoxicosis. The tonsils were infected but there was no previous history of rheumatism.

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ADVANCED MITRAL STENOSIS AT THREE YEARS OLD

BY

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From the Southend General Hospital

Received October 28, 1944

Although rheumatic infection in infancy has been recorded frequently, chronic (healed) rheumatic endocarditis with established mitral stenosis, presenting without manifestations of acute or active carditis, must be exceptional. The following case of a male infant falls into this latter category.

CASE HISTORY

The patient was first seen on May 12, 1942, at the age of 2 years 8 months. The mother stated that for the previous two weeks he had suffered from bouts of spasmodic coughing, accompanied by blueness of the lips and hands, and followed by vomiting and much shortness of breath. In all he had had six such attacks and had become progressively more short of breath, not only during the attacks, but also when at complete rest. His activities had, of his own accord, become steadily curtailed during this period, so that he avoided all forms of exertion, and only with persuasion could he be induced to walk. Further enquiry revealed that the infant had appeared normal in every way, from birth until the age of 21 months, when he began to walk. At this time shortness of breath on exertion was noticed, and the abdomen became unduly prominent. Henceforth development was retarded and he grew but slowly. He tended to be sluggish in habits, avoiding all exertion that might induce breathlessness; otherwise he remained well. Until the present illness this shortness of breath and abdominal distension were not progressive. He had had none of the acute specific fevers, nor was any history of intercurrent illness, such as tonsillitis or sore throat, obtained. Close questioning failed to elicit any history of past rheumatic infection either in the patient or the parents. The mother was a healthy woman of 28 years; she had one other child, aged 2 years. Both pregnancies had been normal and there had been no miscarriages. The father was healthy and had been graded A.1 by a medical board.

On examination the infant lay listless, dyspnœic, and reluctant to move. Undeveloped physically and mentally for his age, the anterior fontanelle was widely open. The face was bloated and pale, with cyanosis of the lips; the extremities felt cold and were also of a dusky hue. The temperature was raised to 101·4° F. and the pulse rate to 130; the rhythm was regular. The apex beat was diffuse but forcible and displaced to the left. No thrill was felt. On auscultation a loud and long grating systolic murmur, maximal in the mitral area, was heard over the præcordium, while a to-and-fro rough and moderately loud murmur was heard in the triscupid area. Examination of the lungs revealed impairment of percussion and diminished air entry at the left base; elsewhere the breath sounds were harsh. The abdomen was notably distended and the umbilicus everted. There was firm hepatic enlargement of four fingers' breadth, but this was not tender, and no ascites was demonstrated.

Since rheumatic heart disease was considered unlikely in one so young, a tentative diagnosis of heart failure, due to congenital heart disease and complicated by whooping cough, was made. The patient was transferred to the Borough Isolation Hospital for further observation and treatment. There the provisional diagnosis of pertussis was confirmed, while the comment on the heart recorded on admission was that "a markedly roughened first mitral sound, resembling an adult presystolic murmur was heard." Shortly after admission overt signs of bronchopneumonia developed. Response to treatment, which included continuous oxygen and chemotherapy, was satisfactory and in spite of a relapse of pneumonia twelve days later the infant was discharged considerably improved, although still breathless, three weeks after admission.

On July 21, nine weeks after being first seen, the patient was again referred to the Southend General Hospital and admitted, having suddenly become gravely ill with rapidly increasing shortness of breath, abdominal distension, and swelling of the legs. On examination there was severe dyspnœa with cyanosis and much swelling of the face and eyelids. Œdema was generalized; the abdomen was considerably more distended than at the first examination, but ascites again could not be detected. Moist sounds were heard at both lung bases, with diminished air entry and impaired percussion note over the left lower lobe. The pulse continued to remain regular; nor was there any significant alteration in the character of the heart murmurs. X-ray of the chest (Fig. 1) showed considerable

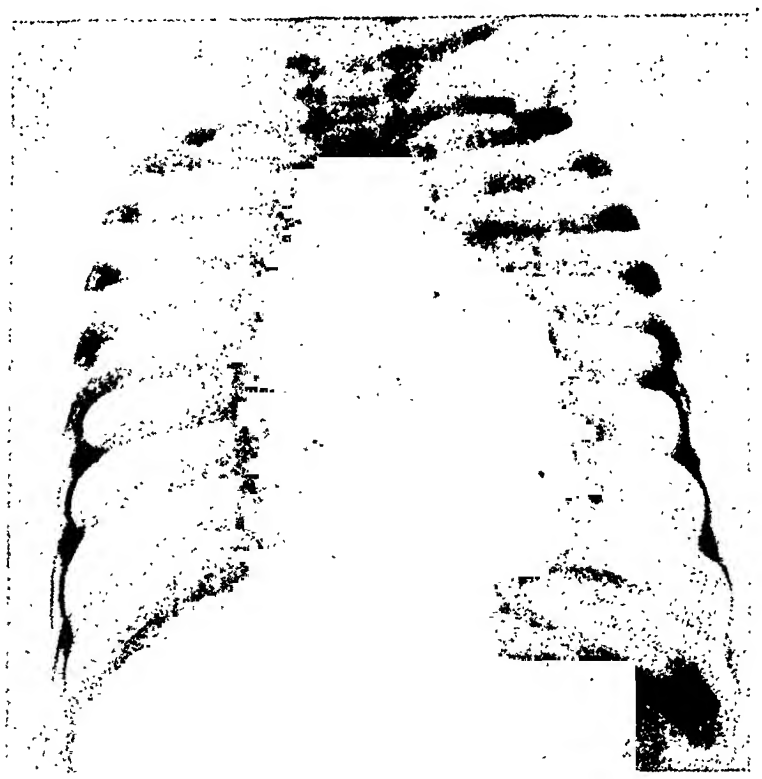

FIG. 1.—Radiogram of chest, showing gross globular enlargement of the heart shadow and marked hilar congestion (27/7/42).

enlargement of the heart shadow, strikingly globular in outline, and gross hilar congestion. The Wassermann reaction was negative.

Death occurred unexpectedly and rapidly, two days after admission. Without warning, the patient vomited with inhalation of the vomitus. Deep cyanosis with urgent dyspnœa immediately ensued, and in spite of prompt treatment by aspiration-bronchoscopy death took place in twenty minutes.

Autopsy Findings

The body was that of an undeveloped but well-nourished infant, swollen by generalized œdema which was most pronounced in the lower extremities, back, and face. Bilateral clear pleural effusions, each of 300 c.c. (10 oz.), were present, and both lungs which showed partial pressure collapse were congested and very œdematous. There were numerous subpleural Tardieu spots.

The heart (Fig. 2) was considerably enlarged and dilated, weighing 98 g. (normal average weight at 2 years 10 months being 60 g. according to Coppoletta and Wolbach, 1933). There were scattered petechial hæmorrhages beneath visceral and parietal pericardium; the pericardial fluid was normal in amount and colour. No trace of old or recent pericarditis was present. The left auricle was greatly dilated and hypertrophied (3 mm. thickness), the endocardium on the posterior wall being thickened and crinkled over an area of 2 cm. × 1 cm. The mitral ring was contracted and narrowed to 1·5 cm. diameter, while the valve cusps were rigid, deformed, and grossly thickened by dense fibrosis without calcification; their margins were fused together except for a narrow slit 1 cm. in length, which was placed at the centre

A B

FIG. 2.—Photographs of the heart.

(A) Shows dilatation of the left auricle, deformity and thickening of the mitral cusps, and narrowing of the mitral ring.

(B) Shows thickening and deformity of the aortic valve cusps, with hypertrophy of the left ventricle, and narrowing of the mitral valve.

of a diaphragm of cartilaginous consistence (" button-hole " stenosis). The chordæ tendineæ were so shortened and thickened as to be unrecognizable. The left ventricle showed considerable hypertrophy (9 mm. thickness) with some dilatation. On section the myocardium appeared normal throughout. The aortic incompetence test was positive, while the aortic valve cusps were rigid, deformed, and partly adherent to each other causing stenosis. The right ventricle and right auricle were dilated and the former was hypertrophied (5 mm. thickness). The tricuspid and pulmonary valves were normal. The foramen ovale was closed, and no patency of the interventricular septum nor any of the recognized forms of congenital morbus cordis was present.

Moderate ascites was present. The liver was hard, slightly shrunken, and the capsule wrinkled, due to recent reduction in size of the organ. On section the parenchyma showed advanced back-pressure changes with secondary fatty degeneration. The spleen and kidneys were firm and congested; the other organs were normal.

Microscopical Examination (Dr. J. R. Gilmour). " A portion of cardiac valve (posterior mitral) shows fibrous thickening and vascularization of cusp (chronic rheumatic endocarditis). There is thickening of the aortic cusp by increase of collagen and spindle fibroblasts; no vessels or inflammatory cells seen in the cusp; a small fragment of attached myocardium is normal, but a little mural endocardium over it, immediately below the valve, is thickened by increase of collagen, fibroblasts, and capillaries. The picture is typical of chronic rheumatic aortic and mitral endocarditis. There is no other endocarditis known that would produce similar scarring. The right ventricular and left auricular myocardium shows hypertrophy; there is no evidence of healed or active rheumatic myocarditis. The liver shows fatty degeneration and central chronic passive congestion."

Discussion

The incidence of rheumatic infection in the first three years of life represents approximately 1 per cent of the total incidence throughout all age groups. The vast majority of this early group occur during the third year, while rheumatic infection before the age of two years is rare. Thus Still (1909) in a series of 1027 cases of rheumatic fever in children found none under two years and eight cases between the second and third year; i.e. less than 0·8 per cent. Among 364 cases of rheumatic arthritis Findlay (1931) recorded none under two years and three cases under three years, while in 457 cases of rheumatic carditis he found two cases occurring in the first two years and four between the second and third year. Finally, McIntosh and Wood (1935) quote collected figures of 2884 cases of rheumatic infection at all ages in which 40, or 1·3 per cent, occurred in the first three years of life.

Although rheumatic infection is uncommon in infancy, it is nearly always accompanied by a severe degree of cardiac involvement, usually of an acute type. McIntosh and Wood (1935) in their series of 24 cases of rheumatic infection in the first three years, found clinical or post-mortem evidence of cardiac involvement in 22, or 92 per cent. However, chronic rheumatic endocarditis with advanced mitral stenosis and congestive heart failure, presenting without manifestations of acute rheumatism and without post-mortem or microscopical evidence of active rheumatic carditis, must be very rare before the third year. Two cases comparable to the present one have been reported by Day (1932) and by McIntosh and Wood (1935). Day's case concerned a female, dying at the age of 24 months; following an attack of "influenza" and otitis media at 10 months, she failed to make progress, and developed heart failure with cardiac enlargement, œdema with pleural effusion, and marked hepatic enlargement at 20 months. At necropsy, the mitral valve was greatly thickened and the orifice reduced to a narrow slit: there was no microscopical evidence of active carditis. McIntosh's and Wood's case (No. 6 in their series) was that of a male, aged 2 years 10 months, who developed bronchopneumonia at 21 months and attacks of generalized œdema with liver enlargement at 26 and 31 months respectively. Death occurred 3 months after the second attack following recurrence of pneumonia. At necropsy the heart weighed 196 g.; the mitral cusps were greatly thickened and nodular with fused verrucæ along the free margins. Microscopic examination showed fibrosis of the myocardium with occasional interstitial accumulation of lymphocytes. The valvular lesions suggested a healed rheumatic process, the authors stating these findings to be unique in their experience. Eigen (1938) and Quinlan (1942) have each reported a case of chronic rheumatic carditis with mitral stenosis at 2 years 8 months. In both instances, however, microscopical examination showed an acute imposed upon chronic endocarditis as distinct from the pure chronic or healed rheumatic process, thus differing in an important respect from our own case and those described above.

It is not surprising that rheumatic carditis in infancy is almost invariably encountered as an acute or active condition and so rarely in the chronic and healed form; for the time factor is against an extensive cardiac lesion becoming healed before the third year, while the ability of the heart muscle to compensate in the young, even for the grossest valvular defect, needs no emphasis, and death from congestive failure alone and opportunities for autopsy are correspondingly rare.

The Possibility of Intra-Uterine Rheumatism

The striking absence of any acute illness prior to the first attendance, the long-standing history of symptoms of heart failure, and the extent of the valvular lesions found at autopsy, all point to an established cardiac lesion with heart failure even before the age of two years, besides making an apparently strong case for intra-uterine rheumatic infection. Although fœtal endocarditis is a possibility that cannot be disproved, there is much evidence that can be marshalled against it in our case. A completely normal pregnancy in the mother and

an absence of any history of rheumatic infection during this period or at any other time in either parent, is strongly opposed to an invocation of intra-uterine rheumatism.

A study of the reported cases of intra-uterine rheumatism reveals that the evidence on which such a diagnosis is based is circumstantial and rests on two observed facts: active rheumatic infection during pregnancy, and similar manifestations in the offspring immediately following or in the first few weeks after birth. Two of the most convincing cases reported are those of Kissane and Koons (1933) and of Ferguson (1893). In Kissane's and Koon's case the mother had had recurrent rheumatic fever since the age of 12 years; a cardiac lesion had been noticed at 20 years, and she had suffered from active rheumatic fever with swollen joints throughout her entire pregnancy at the age of 25 years. The infant was born with red painful joints and 30 hours after birth abnormal cardiac sounds were heard. Joint symptoms and dyspnœa persisted for six months. Death occurred at 9 years when pan-valvulitis and gross mitral stenosis was proved at autopsy. Ferguson's case developed acute rheumatic fever with joint involvement 10 days after birth, the mother having suffered from severe rheumatic fever from the second month of pregnancy.

Whereas much attention is paid, and even undue weight attached, to a past history of rheumatic fever in the diagnosis of mitral disease, many patients with established rheumatic endocarditis tender no such history. Conversely, a large number and perhaps the majority who give a history of rheumatic infection in the past, have no demonstrable cardiac lesion at the time of examination. It is frequently the case in the adult that the most extreme, that is the most chronic and insidously progressive cases of mitral stenosis are those that give no history of acute rheumatic fever nor chorea, but in contra-distinction develop a slow relentless sclerosis of the mitral valve structures without acute endocardial changes. Tight " button-hole " stenosis with narrowing of the mitral ring is the relatively outstanding feature in such cases, unrevealed in some instances until the onset of failure, in contrast with the greater tendency to pancarditis and deformity with beading of the valve cusps in cases with a history of recurrent acute rheumatism, the form seen most commonly in children and young adults. It is the former or " adult " type of lesion that is portrayed by our own case. The most likely explanation, therefore, which would account for the extreme degree of mitral stenosis noted in the present case, is that the rheumatic infection was acquired, developing some time after birth as a pure cardiac lesion, and that the patient entered as a very junior member that large group of older people whose hearts are silently but permanently damaged by one of the subtlest and most incapacitating diseases known to medicine.

Summary

A case of chronic (healed) rheumatic endocarditis with advanced mitral stenosis in an infant aged two years and ten months is reported, together with the autopsy findings.

We wish to thank Dr. J. R. Gilmour for permission to record the morbid histology findings in this case, and Dr. R. B. Christie for clinical information while the patient was under his care.

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HEART BLOCK FOLLOWING DIPHTHERIA

BY

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From the Royal Northern Infirmary, Inverness

Received August 16, 1944

In 1943 when reporting a case of congenital heart block with dextrocardia (Leys, 1943) I discussed the differential diagnosis of acquired and congenital heart block. It was remarked that complete heart block due to diphtheria (and probably other infections also) was almost always fatal, and that nearly all cases of complete heart block in children and young adults were congenital. Fishberg (1940) with his very extensive practice, had seen only one patient surviving the appearance of complete heart block in diphtheria: he referred to a study by Stechner in 1928 of 19 cases, all fatal, and to a study by Jones and White in 1927 of 100 patients after severe diphtheria, none of whom had evidence of heart disease at the time of their examination. Hoskin (1926) found various minor post-diphtheritic cardiographic changes in 16 cases following severe attacks, but found no conduction defects.

I now report a case of complete dissociation of auricle and ventricle in a married woman of 25 who had severe diphtheria at the age of 10 with palatal and ocular palsies. She reports that her heart was said to have been affected at that time, and that it was later remarked to her, when she had cerebrospinal fever at the age of 22, that she had a slow pulse. No comment on her pulse rate was made when she had appendicectomy at a cottage hospital at the age of 18.

She was referred to the Royal Northern Infirmary, Inverness, because of attacks of syncope; these had began to appear shortly after an illness in which she had sore throat and joint pains. She remained in bed for only a few days. A similar illness had occurred two years previously. The attacks consisted of a choking sensation in the throat, pain and a tight sensation in the chest, followed by transient loss of consciousness, and later by vomiting.

The heart rate at rest is either 36 or 48; other rates are not found. After exercise it rises

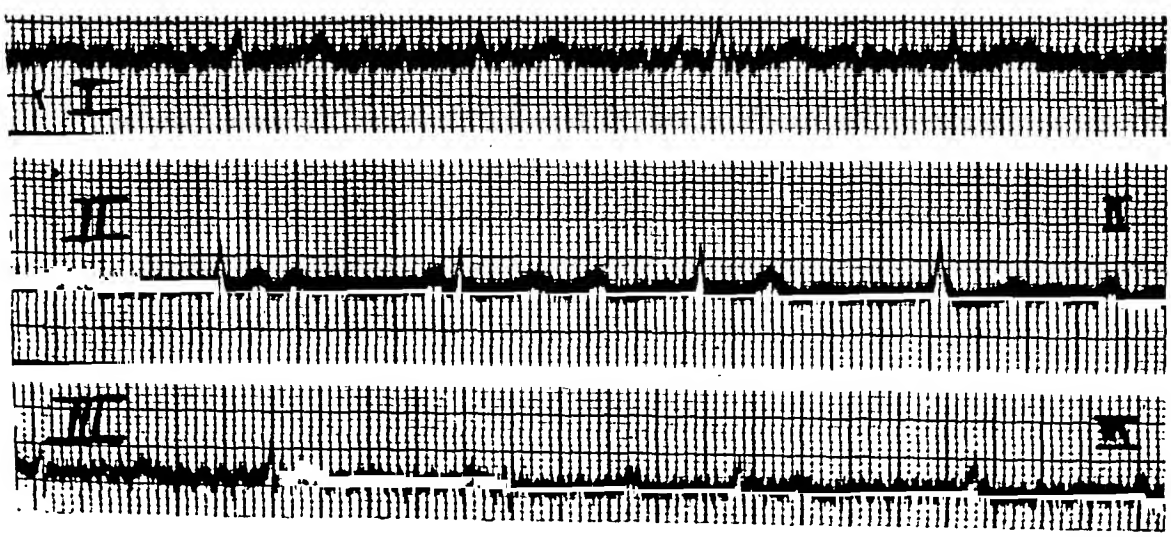

FIG. 1.—Electrocardiogram, showing complete heart block: auricle, 86; ventricle, 60 a minute; after exercise.

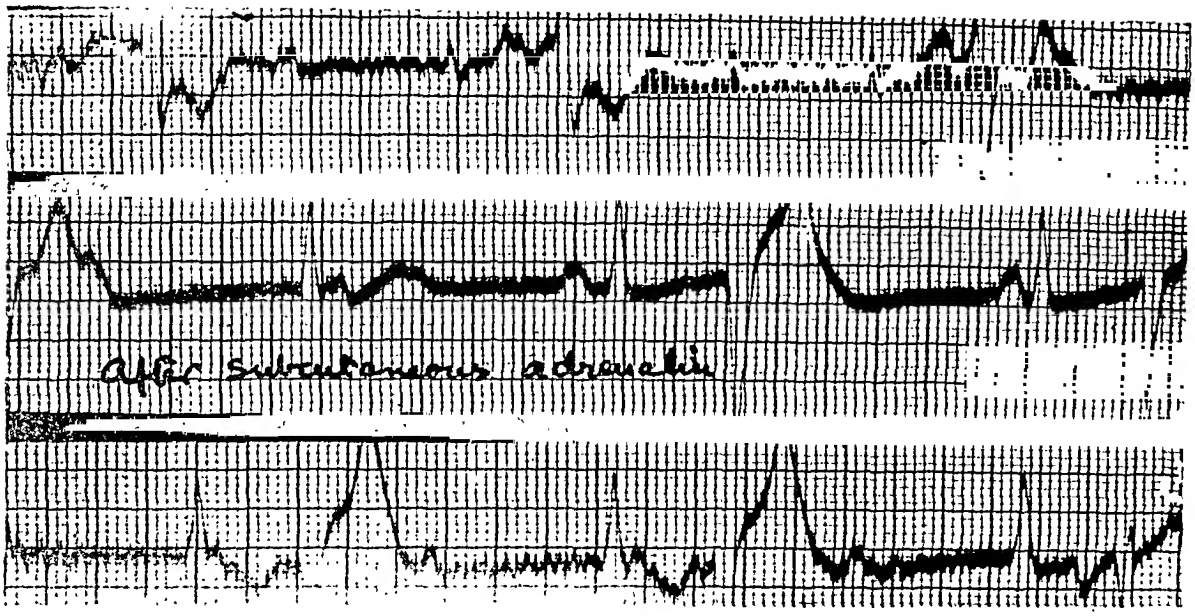

FIG. 2.—After subcutaneous injection of adrenalin showing frequent ventricular extrasystoles: auricular rate about 75; ventricular rate about 48 when no extrasystoles.

to 60. It is not influenced by subcutaneous injection of 1/100 of a grain of atropine sulphate. Ventricular extrasystoles appear after exercise and after subcutaneous injection of adrenalin. These extrasystoles alternate with regular beats for 10 to 20 cycles at a time. X-ray screening shows slight enlargement of the left side of the heart. Clinically, the heart does not appear enlarged, with the apex beat three and a half inches from the midline. There are no murmurs. The blood pressure is 150/90. The pulse is dicrotic. The cardiogram shows complete dissociation of auricle and ventricle, but otherwise is normal except for the appearance of the ventricular extrasystoles. These are not present when she is at rest. There is a complete absence of all tendon jerks throughout the body.

SUMMARY

The evidence for this case of complete heart block being due to diphtheria is:

(1) that she had severe diphtheria with neuritis at the age of 10 years;
(2) that subsequently a slow pulse was reported at the age of 22 years; and
(3) that she has complete absence of all tendon jerks without other evidence of nervous system disease.

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AURICULAR FIBRILLATION AND AURICULAR FLUTTER IN DIPHTHERIA

BY

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Auricular fibrillation and auricular flutter are generally regarded as uncommon heart disorders in children—a fact that is illustrated by their omission from many textbooks of pædiatrics. Auricular fibrillation develops in mitral stenosis due to rheumatic involvement of the heart, when it appears generally after the age of puberty; but it can occur in children of all ages in the course of a severe acute infectious disease, especially diphtheria. The reports of auricular fibrillation and auricular flutter occurring in diphtheria are not numerous: Burkhardt (1938) could not detect one case of auricular fibrillation amongst 140 cases of diphtheria examined electrocardiographically every second or third day; Bourne (1941) described one case of diphtheritic myocarditis with auricular flutter in a woman aged 79 years; Campbell *et al.* (1943) reported a case of transient auricular fibrillation in a youth of 22 years. Another report, Neubauer (1942), recorded three cases of auricular fibrillation in a series of 100 cases of diphtheritic heart disorders in children.

Altogether 6 cases of auricular fibrillation among a series of 200 cases of diphtheritic myocarditis have now been observed between June, 1941, and June, 1944, that is an incidence of 3 per cent. It occurred in 5 children and 1 adult: their ages were 2 years and 5 months, 2 years and 9 months, 6, 8, 10, and 28 years. The auricular fibrillation was associated with severe myocarditis and in all cases an involvement of the conducting system was found by cardiographic records. Partial auriculo-ventricular block was found in four patients and complete block in the other two, whose ages were 2 years and 5 months, and 6 years. The heart action was found slow (40–75 a minute) and irregular in partial A-V block and slow and regular in complete heart block. Examples are given in Fig. 1 and 2. The chief clinical signs observed were as follows:

	Cases		Cases
Syncope	2	Engorged jugular veins	2
Vomiting	4	Enlarged liver	2
Cyanosis	3	Severe albuminuria	4
Enlarged cardiac dullness	4		

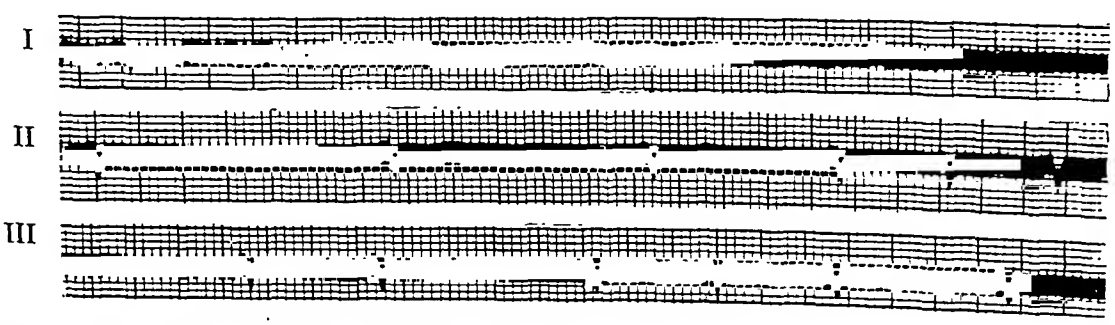

FIG. 1.—An example of auricular fibrillation with slow ventricular rate. The ventricular rate is about 50 a minute. QRS is of low voltage; S-T–T is almost isoelectric. The slow ventricular rate indicates some degree of partial A-V block. (D. E., 2 years and 9 months old, twelfth day of diphtheria.)

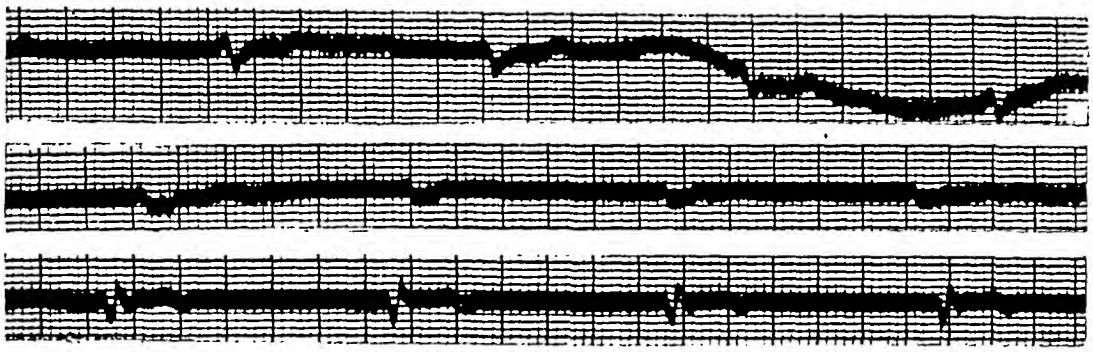

FIG. 2.—An example of auricular fibrillation with complete A-V block. The ventricular rate is about 49 a minute, regular. QRS is splintered and notched, of Q-type in lead III, and of low voltage, with a duration of 0·14 sec. T is small in leads I and II and inverted in lead III. (J. W., 2 years and 5 months old, eleventh day of diphtheria.)

The blood pressure was diminished in all instances, and the lowest readings were 56/30 in the child 10 years of age. Four patients died, two recovered. The adult made a complete recovery from a partial A-V block: she developed palatal, pharyngeal, facial, and hypoglossal paralysis and peripheral neuritis of the legs in the course of the disease and she was discharged after three and a half months. The other patient who recovered was the girl of six with complete heart block, palatal and pharyngeal paralysis, and peripheral neuritis of the legs; she was discharged with no clinical signs present in her heart and with an almost normal cardiogram after three months. The death occurred in one patient 2 years and 5 months old (Fig. 2) on the eleventh day of disease; two children, 2 years and 9 months and 8 years of age, died on the sixteenth day of disease, and another patient of 10 years died on the forty-fourth day of the disease.

To supplement the limited number of reports on auricular fibrillation and auricular flutter in childhood, the following account of a case is given, with clinical, cardiographic, and pathological findings.

History. L. A., aged 5 years. Previous diseases; chicken pox in 1941 and measles in 1943. The child had not been inoculated against diphtheria. On May 12, 1944, she began to vomit, developed a sore throat and a slight croupy cough, and was admitted to hospital two days later.

On admission the picture was not one of a very ill child. Examination revealed the presence of œdema in the throat and membrane covering both tonsils; enlarged cervical glands and oral fœtor were noted. A bacteriological examination of the throat swabs showed the presence of *C. Diphtheriæ* and *S. Hæmolyticus.* The child was given 20,000 units of diphtheria antitoxin. A regular tachycardia was present at this stage, the heart sounds being normal.

The course of the disease was as follows:

May 18 (7th day of the disease). A punctate rash appeared on the trunk, the throat was highly inflamed, and the tongue was peeling at the tip and on the edges.

May 20. Severe albuminuria, a sign of bad prognosis, manifested itself. Tachycardia persisted.

May 21. Red strawberry tongue. The first apical heart sound was found to be diminished in intensity; the pulse rate was 124 and the blood pressure 65/35. The child was restless and the general condition had deteriorated, the colour being poor. Blood sedimentation rate 21 in the first hour.

May 24. The child presented some cyanosis of the lips and distended jugular veins. The pulse was weak and irregular, the rate varying between 136–150. The heart action was irregular, the rate being 160–180 (Fig. 3).

May 25. Her condition was progressively worse. The pulse was soft, with a rate of about 160 (Fig. 4). The abdomen was slightly distended and the liver dullness increased.

May 26. The heart action appeared to be regular and the rate slower. The blood pressure was 85/50, but the child was very restless and seemed to be having pain in the precordial region. The cardiographic findings were similar to those demonstrated in Fig. 4 showing auricular flutter with 2 : 1 block.

May 27 (16th day of disease). The child died.

Post-mortem findings (Professor Bernard Shaw). Heart weighs 104 grams. The pericardial sac contains a normal amount of free fluid. There is no pericarditis. The right auricle is slightly dilated and contains post-mortem thrombus. The foramen ovale is closed. The tricuspid valve admits two fingers and the cusps are thin and delicate. The right ventricle is not dilated, the muscle

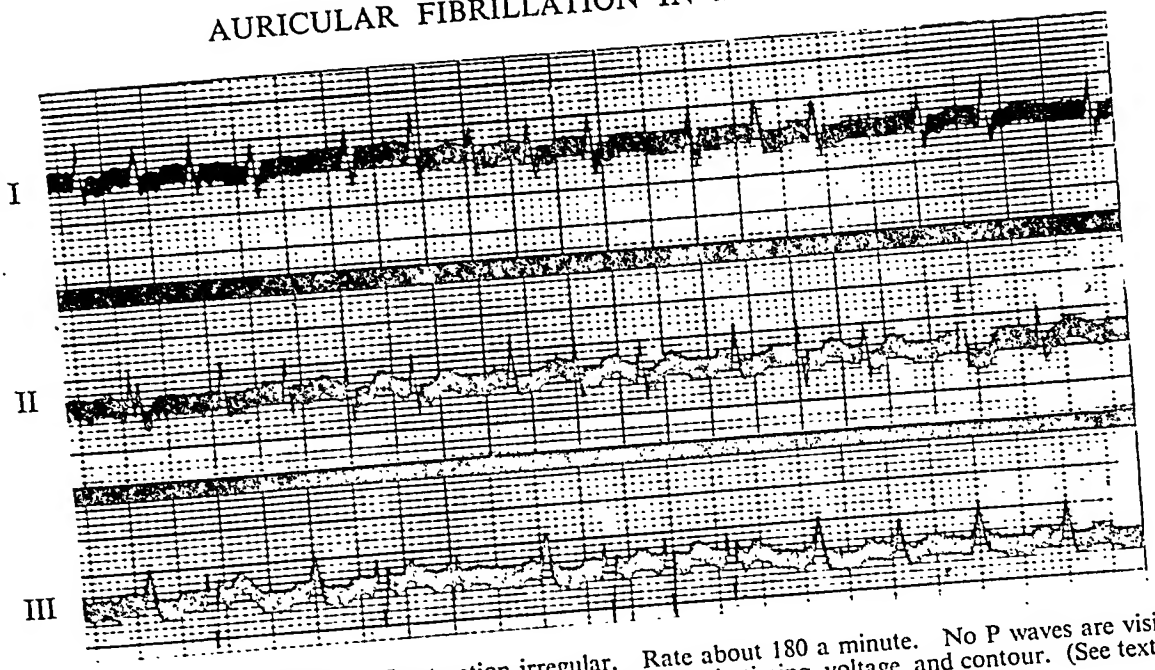

FIG. 3.—Auricular fibrillation. Heart action irregular. Rate about 180 a minute. No P waves are visible. Fine undulations between the ventricular deflections, irregular in timing, voltage, and contour. (See text.)

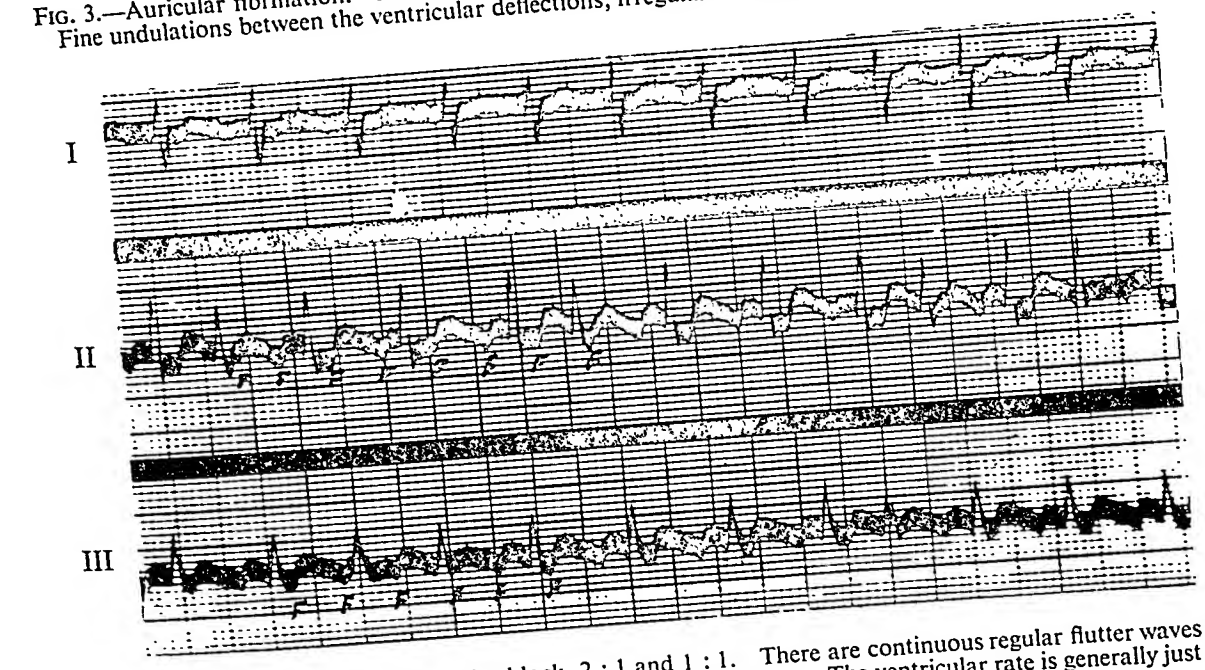

FIG. 4.—Auricular flutter with irregular block, 2 : 1 and 1 : 1. There are continuous regular flutter waves (F), best seen in lead II and III, occurring at the rate of 260 a minute. The ventricular rate is generally just half as rapid, 130 a minute.

being 0·4 cm. in thickness at the base. The pulmonary artery is smooth and elastic. The left auricle contains post-mortem clot and the wall is slightly thicker than usual. The mitral valve admits one finger and the cusps and chordæ tendineæ are thin and delicate. The left ventricle is dilated and the muscle measures 0·9 cm. in thickness at the base. The aortic valve is normal. The aorta shows some hæmoglobin stain. The coronary arteries are patent and free from atheroma. The myocardium is pale; there are no hæmorrhages and no evident fatty changes.

Histology. Sections of right auricle, tricuspid valve, right ventricle, left auricle, mitral valve, and left ventricle: these sections show an acute myocarditis involving the musculature of both auricles and both ventricles, but more marked in the left auricle and left ventricle; with regard to the latter the lesions occur with equal frequency at all levels.

The lesions consist of multiple small cellular foci consisting of mobile histiocytes, a few polymorphs, and eosinophils, situated in the stroma, but with no evident relation to the vessels. The muscle fibres show no necrosis and no fatty change. Hidden in the bays between the columnæ carneæ of the right auricle are multiple mural ante-mortem thrombi probably induced by fibrillation.

The lesions might be due either to diphtheria or scarlatina as there is no histological differentiation between the two.

Discussion

On clinical and bacteriological grounds, the case was one of faucial diphtheria. Hæmolytic streptococci are not uncommonly found in diphtheritic throat lesions caused by *gravis* strain, and in the case under discussion the presence of hæmolytic streptococci, in addition to the development of a rash and strawberry tongue as described above, indicates beyond doubt a double infection. The persistent tachycardia and the diminished intensity of the first apical sound, the lowered blood pressure, and increased blood sedimentation rate were clinical manifestations of a myocarditis. Auricular fibrillation, detected clinically and cardiographically three days later, confirmed the presence of myocarditis; it persisted for two days in spite of digitalis therapy and ultimately changed to auricular flutter. Anatomical and histological findings at autopsy revealed an acute myocarditis with formation of ante-mortem mural thrombi.

Here, then, is an example of auricular fibrillation and auricular flutter developing as terminal events in the course of an extremely acute myocarditis.

It is with the kind permission of Professor Bernard Shaw that the detailed post-mortem notes are included with the present report.

My thanks are also due to Dr. I. E. McCracken, M.O.H., Newcastle upon Tyne, and to Dr. G. Hurrell, Medical Superintendent, City Hospital for Infectious Diseases, Newcastle upon Tyne, for facilities provided.

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HEART BLOCK AND THE SIMULATION OF BUNDLE BLOCK IN DIPHTHERIA

BY

HAROLD COOKSON

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Cardiographic studies in diphtheria show that a wide variety of arrhythmias and abnormalities of pattern occur. Among these heart block is familiar, not so much because it is common, but because in its more severe forms it indicates a grave prognosis. Burkhardt, Eggleston, and Smith (1938) recorded 11 cases of A-V dissociation, all fatal; some presented a terminal ventricular tachycardia. They noted a high idio-ventricular rate of 80–90 so that block was not suspected before the cardiogram was taken.

Alstead (1932) found the P–R interval to exceed 0·2 sec. only once in 100 cases, although in 10 others this interval increased during the disease: two of his cases said to show complete block died; but the tracing of one of these is not convincing. Stecher (1928–29) studied 19 cases of complete block in diphtheria; all died. He publishes tracings of 11 cases; four of these show complete block, but of the remainder four show ventricular tachycardia and one normal rhythm with bigeminy. Nathanson (1928) described T wave changes in 7 cases, but noted no conduction changes; his Case 3 does, however, show a wide QRS. Friedemann (1932) found the ventricular rate high in complete block, but did not note so high a mortality as most other authors, in this condition. Begg (1937) had a mortality of 66 per cent in both bundle branch block and complete block. (One of his records said to show complete block, where the auricular rate is 100 and the ventricular 135, should perhaps be regarded as ventricular tachycardia.) Harries and Mitman (1941) state that partial block is rare, that left bundle block is commoner than right, and regard A-V block as a serious sign. On the other hand Neubauer (1942) found partial block in 17 per cent of cases (but his Fig. 10 described as showing 3: 1 block seems to show complete block) and complete block in 5 per cent. He also records auricular fibrillation associated with complete block. However, his Fig. 17 suggests complete block with normal auricular mechanism, not fibrillation; nor is auricular fibrillation evident as claimed in Fig. 14.

Present Investigation

Eighty-three cases of diphtheria were investigated clinically and serial cardiograms taken at intervals throughout the illness. About 300 cardiograms were taken in all, 2 or 3 in mild cases, more in the severe ones. In 63 of the patients the cardiogram was abnormal, that is in 76 per cent. Ten of these showed some defect of conduction; the others inversion of T in one or more leads; in less severe cases T was usually inverted in lead III only; in severe cases the inversion was seen in more than one lead, sometimes in all four. Displacement of the S–T segment was frequent, and nearly always downwards. Other abnormalities commonly seen were axis shift, slurring and slight widening of QRS, and bizarre P waves. Conduction changes were relatively uncommon; there was increase in the auriculo-ventricular conduction time in four, but in only one of these did it exceed 0·2 sec. In two of these there were also changes in the T waves. Bundle branch block with increase in P–R was recorded in three cases, and complete block in one: all these four patients died. Three other patients without block died, one during ventricular tachycardia, one from nervous lesions when his cardiogram had returned to normal, and one showing T changes and low voltage. The

mortality for the whole series was thus 8·4 per cent. There was no fatality over the age of 12, and none in an immunized subject.

Only ten cases are reported here, but they have been followed closely throughout their course in hospital, by the same observer, both clinically and cardiographically, and in all fatal cases necropsies were carried out and histological studies made.

Case Reports

Increase in P–R Interval

Case 1. J. R., age 7. Antitoxin on 8th day; pharyngeal and nasal diphtheria. 30th day, vomiting. 53rd day, palatal palsy. 83rd day, apparently quite well; EC. (electrocardiogram), N.R., rate 120; P–R, 0·18 sec.; T III just negative. 99th day, EC., N.R., rate 110; P–R, 0·15 sec.; T III flat. 111th day, EC., N,R., rate 90; P–R, 0·15 sec.; T III positive.

Case 2. M. D., age 18. Antitoxin on 7th day; pharyngeal diphtheria. 7th day, EC., N.R., rate 110; P–R, 0·16 sec. 13th day, EC., rate 75; P broad and bifid; P–R, 0·18 sec. 25th day, EC., N.R., rate 115; P–R, 0·2 sec. 32nd day, EC., N.R., rate 85; P broad and bifid; P–R, 0·18 sec. No complications in nervous system, nor clinical signs or symptoms of myocardial injury throughout.

Case 3. Mrs. G., age 24. Antitoxin on 6th day; pharyngeal diphtheria. 7th day, EC., N.R., rate 125; P broad and notched; P–R, 0·2 sec.; right axis deviation; B.P. 125/80. 60th day, EC., N.R., rate 65; P–R, 0·15; rate 100 with deep breathing; P–R increasing to maximum of 0·2 sec. No symptoms.

Case 4. J. G., age 8. Antitoxin on 6th day, immunized 18 months before; nasopharyngeal diphtheria. 8th day, EC. (Fig. 1A), N.R., rate 105; P–R, 0·15 sec.; slight depression of S–T in leads II and III. 22nd day; general condition good, no complications in nervous system; apex beat in mid-clavicular line fourth interspace; sounds normal at apex; wavy systolic pulsation to left of sternum in second and third interspaces; systolic murmur and second sound duplicated at pulmonary area; B.P. 95/55; liver edge three-quarters of an inch below right costal margin; EC. (Fig. 1B), N.R., rate 100; P–R, 0·2 sec., S–T depression in leads I, II, and IVR; elevation in III; T diphasic in II and IVR, negative in III. 32nd day, EC., N.R., rate 85; P–R, 0·2 sec.; T now positive in leads II

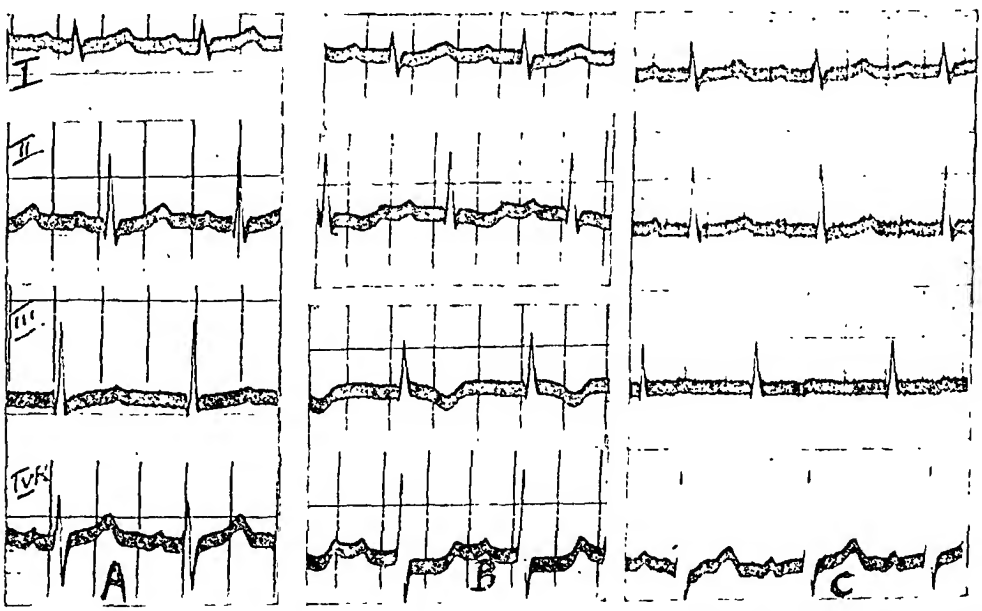

Fig. 1.—Case 4. Development of long P–R interval. (A) 8th day. (B) 22nd day. (C) 5 months later. See text.

and IVR and less negative in III; cardiac signs as before except that a faint blowing diastolic murmur was audible in the third interspace near the sternum. Discharged from hospital on the 80th day. On re-examination 3 months later, child seemed quite well; apex beat just outside mid-clavicular line; wavy precordial systolic pulsation; short rough diastolic murmur at apex in lying position; faint blowing diastolic murmur in third left interspace; B.P. 110/60; on radioscopy, pulmonary arc prominent, left ventricular contour slightly prominent, and left auricle not enlarged; EC., N.R., rate 90; P–R, 0·21 sec.; T III negative. The signs indicated that mitral stenosis and aortic incompetence were present and that rheumatic carditis had occurred some time before the attack of diphtheria. Examination 2 months later (5 months after discharge from hospital) showed no change in

physical or radioscopic signs; cardiogram (Fig. 1c) showed the P–R interval to be still 0·21 sec.; T inversion in lead III less and R in lead IVR of greater amplitude.

Prolonged P–R and Bundle Branch Block

Case 5. V. F., age 3. Antitoxin on 3rd day. Faucial diphtheria; B.P. 95/55. 7th day no clinical signs or symptoms of circulatory failure; B.P. 70/50; EC. (Fig. 2A), N.R., rate 105; P–R, 0·18 to 0·2 sec.; right bundle branch block (B.B.Bl.) but alternate beats in lead II show no B.B.Bl. 8th day vomiting and collapse. 9th day: B.P. 60/30; apex beat visible half an inch outside mid-clavicular line; heart sounds normal; liver edge one inch below right costal margin; EC. (Fig. 2B), N.R., rate 65; bundle branch block; P bifid or wavy; P–R, 0·3 sec. 11th day, died.

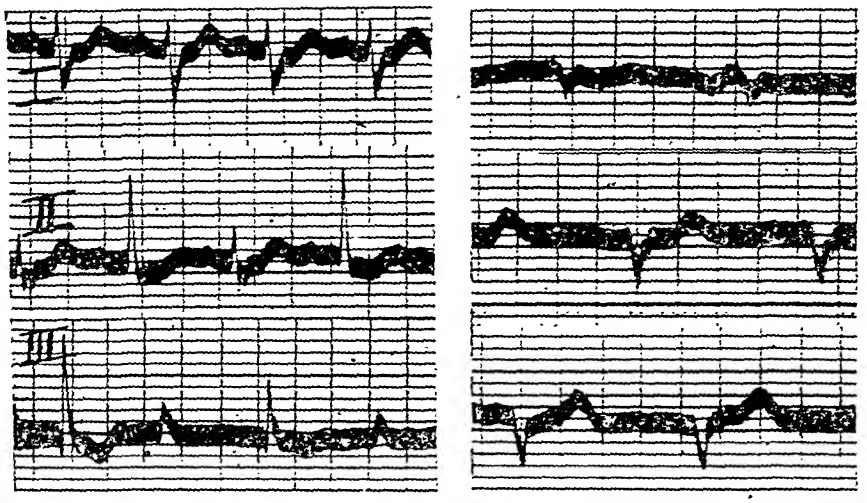

FIG. 2.—Case 5. Development of long P–R interval and bundle branch block. (A) 7th day. (B) 9th day. See text.

Necropsy. Left auricle contains adherent thrombus: on section, muscle fibres necrotic and œdematous. Right ventricle on section, degeneration of muscle; congestion and cellular infiltration. Left ventricle, on section, areas of advanced degeneration; some early fibrosis. Liver: intense venous congestion; necrosis in central part of lobules.

Case 6. A. G., age 12. Antitoxin on 2nd day (26 hours after onset). Faucial diphtheria, bull-neck, heavy albuminuria. 3rd day, apex beat difficult to feel, probably in mid-clavicular line; sounds normal; B.P. 95/70; EC. (Fig. 3A), N.R., rate 120, sinus arrhythmia; S–T depression in leads II and III; QRS, 0·07 sec.; P peaked in leads II and III, P–R, 0·12 sec. 8th day, swelling of neck almost gone; able to take light solid diet; palatal palsy; apex beat within mid-clavicular line, fourth interspace; systolic retraction in third left interspace; sounds normal; B.P. 80/60; liver not felt;

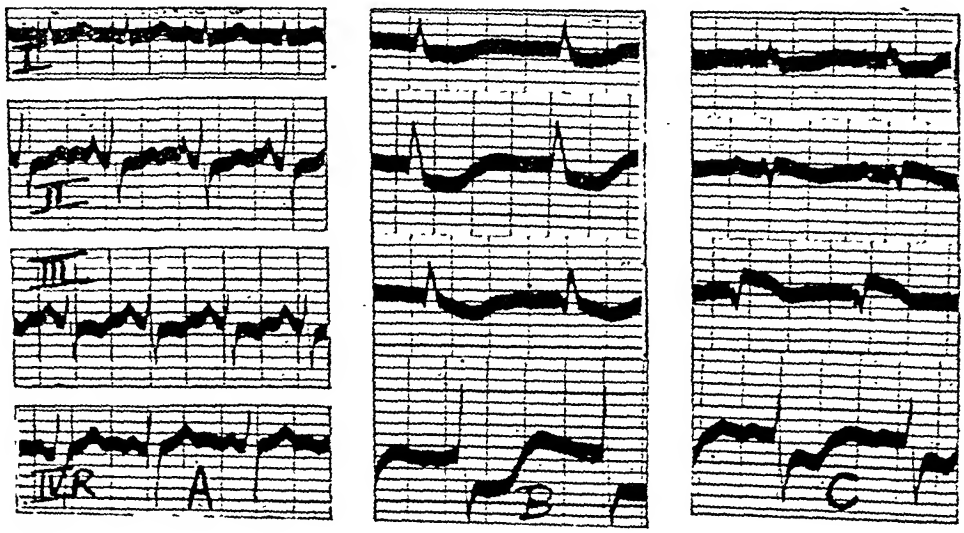

FIG. 3.—Case 6. Lengthening of P–R interval and widening of QRS complexes. (A) 3rd day. (B) 8th day. (C) 10th day. See text.

knee and ankle jerks present; EC. (Fig. 3B), regular rhythm rate 80; P wave not seen; QRS, 0·1 sec.; S–T depression in all leads. 10th day, vomiting; first sound very distant; second well heard; B.P. 70/60; jugular vein well seen, but not above level of second costal cartilage; liver not palpable; trace of albuminuria; EC (Fig. 3C), N.R., rate 90; P–R, 0·18 sec.; S–T deviation downwards in leads I and IVR, upward in II and III; QRS, 0·1 sec. Died suddenly two hours later after incision for intravenous infusion.

Necropsy. Heart: weight, 175 g.; left ventricle maximum thickness 1·2 cm., minimum 0·7 cm.; right ventricle, maximum thickness 0·5 cm.; 15 c.c. clear yellow fluid in right pleura, 7 c.c. in left pleura. On section, myocardium showed congestion, œdema, degeneration up to stage of necrosis, and cellular infiltration mainly with plasma cells, in all chambers, most in left ventricle; areas of intense congestion and cellular infiltration in pericardium. Liver: enlarged, edge reaching to within a quarter of an inch of umbilicus; on section, venous congestion, necrosis in central and mid-portions of lobules. Kidney: venous congestion; degeneration of tubular epithelium. Lung: areas of collapse and œdema separated by areas of emphysema.

Case 7. B. E., age 3. First antitoxin on the 5th day of the disease; faucial diphtheria. 6th day: apex beat fourth interspace not outside mid-clavicular line; sounds normal and well heard; B.P. 90/65; EC., N.R., rate 135, slight right axis deviation; P high voltage; P–R, 0·15 sec.; T III flat; T in IVR low voltage and diphasic. 7th day: triple rhythm at apex on inspiration; B.P. 90/70; EC. (Fig. 4A) as on previous day but rate 125. 9th day: triple rhythm at apex; B.P. 95/55; liver palpable and tender; slight dyspnœa; vomited once; heavy albuminaria. EC., N.R., rate 110; left bundle branch block; P–R, 0·18 sec. (Fig. 4B). 10th day, neck swelling almost gone; vomited once; apex beat not felt; triple rhythm at apex; B.P. 90/60. EC. (Fig. 4C), N.R., rate 110; L.B.B.Bl. but QRS altered since previous tracing; occasional supra-ventricular premature beat.

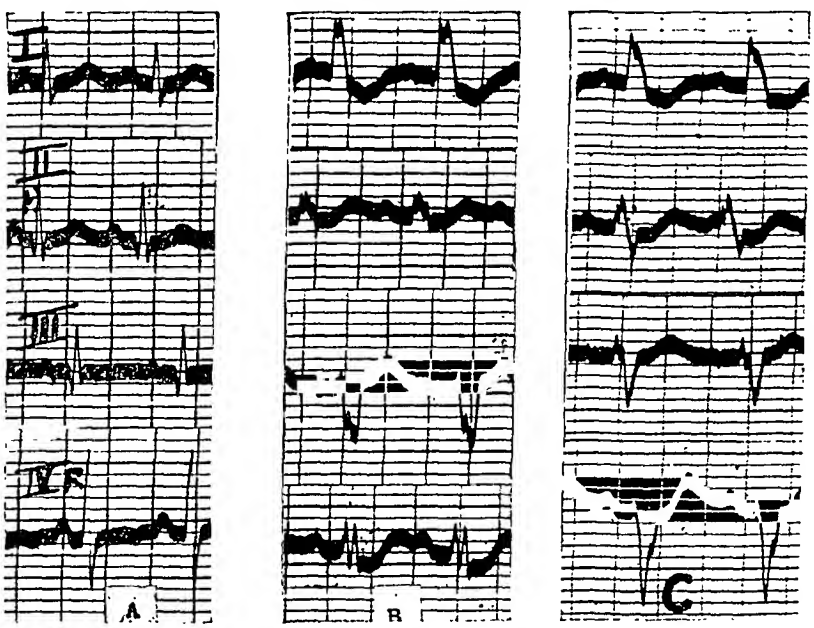

FIG. 4.—Case 7. Lengthening of P–R interval and development of bundle branch block. (A) 7th day. (B) 9th day. (C) 10th day. See text.

11th day, vomiting, pain over liver, which is increasing in size; apex beat fifth space within mid-clavicular line; triple rhythm not heard; B.P. 80/45; EC., N.R., rate 95; irregularity due to sinus arrhythmia, nodal escape and interference dissociation; P–R, 0·1 to 0·3 sec., L.B.B.Bl.: same day, 6.30 p.m., having intramuscular glucose-saline; B.P. 75/45; liver still larger; EC. similar to previous tracing but P flatter, and P–R up to 0·38 sec. 12th day: vomiting; nasal regurgitation; diffuse precordial pulsation; no apex beat palpable; shallow occasional sighing respiration; no signs in lungs; deep reflexes present; B.P. 65/45; EC. (Fig. 5), N.R., rate 90; sinus arrhythmia and nodal escape; bundle branch block of S type and of R type according to whether sinus or nodal rhythm is present; S–T depression in all leads. 13th day, vomiting, restlessness, pallor, constant sighing; apex beat not palpable, but visible in fourth and fifth interspaces and extending just outside mid-clavicular line; sounds distant; systolic murmur at apex; liver larger; B.P. 55/40, no signs in lungs. EC. (Fig. 6A), N.R., rate 105; P–R, 0·15 sec., bundle branch block of indeterminate type; 1/200 of a grain of atropine was given intramuscularly and ten minutes later the cardiogram had altered, becoming similar to the latter part of the tracing of the previous day; it shows nodal rhythm rate 92 and R.B.B.Bl. (Fig. 6B). Triple rhythm with audible third sound (Evans' type I B) was heard after the injection of atropine. 9.30 p.m., constantly sighing and crying out; radial pulse not palpable and B.P. not obtainable. EC. (Fig. 6C); nodal rhythm, rate 90; P not visible; R.B.B.Bl., QRS wider than in previous tracing; S–T depression all leads. Died two hours later.

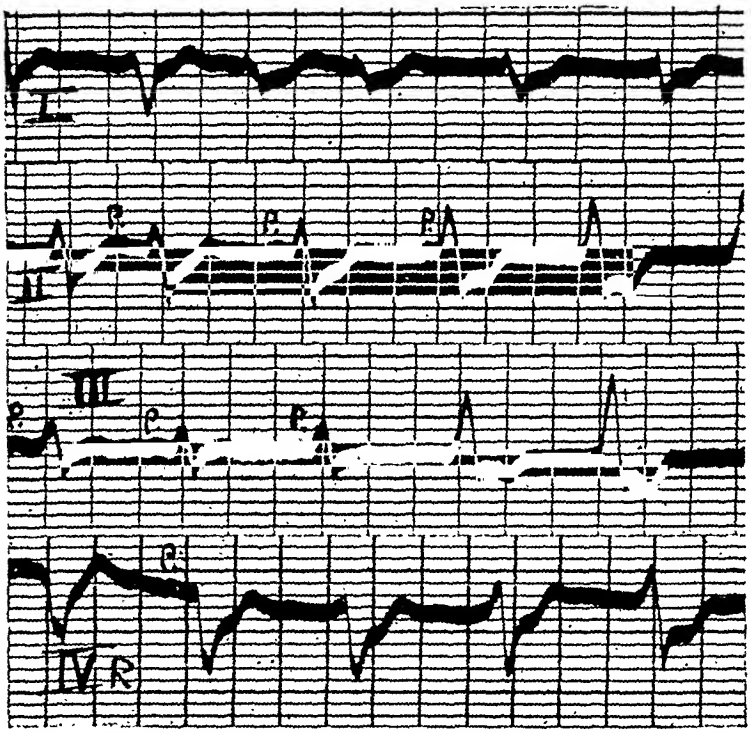

FIG. 5.—Case 7. Sinus arrhythmia and nodal escape with bundle branch block of varying type. 12th day. See text.

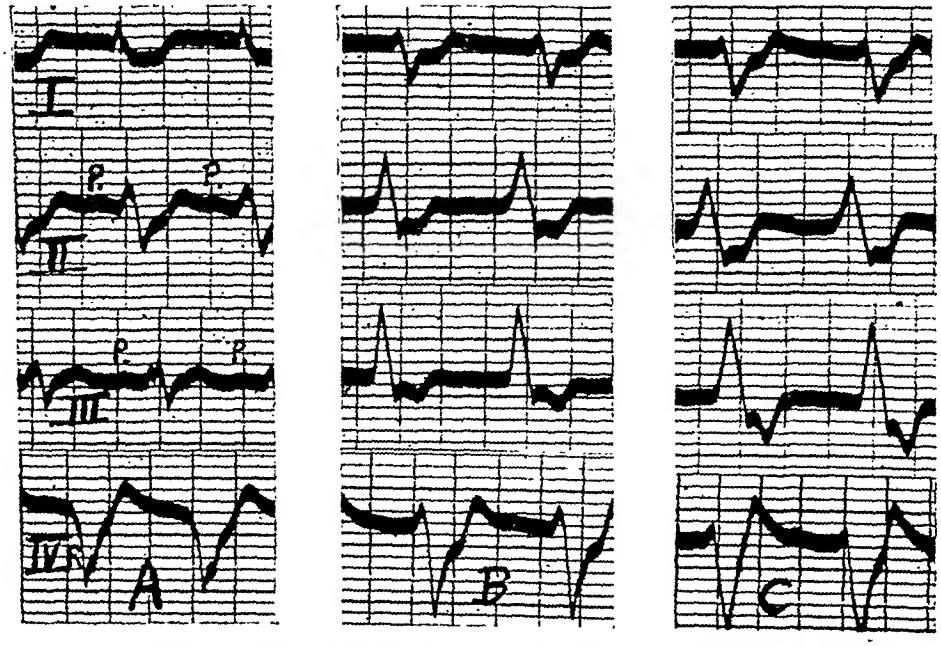

FIG. 6.—Case 7. Bundle branch block of varying type. All 13th day. See text.

Necropsy. Straw coloured effusions in both pleuræ, 450 c.c. in right, less in left; liver enlarged. Heart: weight 110 g.; left ventricle, maximum thickness 9 mm., minimum 3 mm.; right ventricle, maximum thickness 5 mm., minimum 2 mm.

Histology. Lungs: collapse, œdema and emphysema. Liver: marked venous congestion; advanced fatty degeneration; areas of necrosis. Heart: little normal muscle remains; advanced degeneration in all sections; areas of necrosis; œdema; a little fibrosis in left auricle and left ventricle.

Complete Heart Block

Case 8. M. L., age 8. First antitoxin on 3rd day; faucial and nasal diphtheria. 4th day: apex beat within mid-clavicular line; sounds normal; B.P. 100/50; EC. (Fig. 7A), N.R., rate 140,

right axis deviation; P–R, 0·1 sec.; slight S–T depression all leads. 6th day, vomiting and heavy albuminuria; apex beat in mid-clavicular line; sounds normal; B.P. 75/45; no liver signs; EC. (Fig. 7B) lead IVR only; rate 150; P–R, 0·15 sec., QRS, 0·12 sec. 8th day, vomiting blood; apex beat not palpable, sounds normal; petechiæ and ecchymoses in skin; EC. (Fig. 7C). Complete heart block, auricular rate 140 with sinus arrhythmia; ventricular rate 115; R.B.B.Bl.; S–T depression in all leads. 9th day, dyspnœa, vomiting; apex beat not felt; sounds normal; B.P. 60/0;

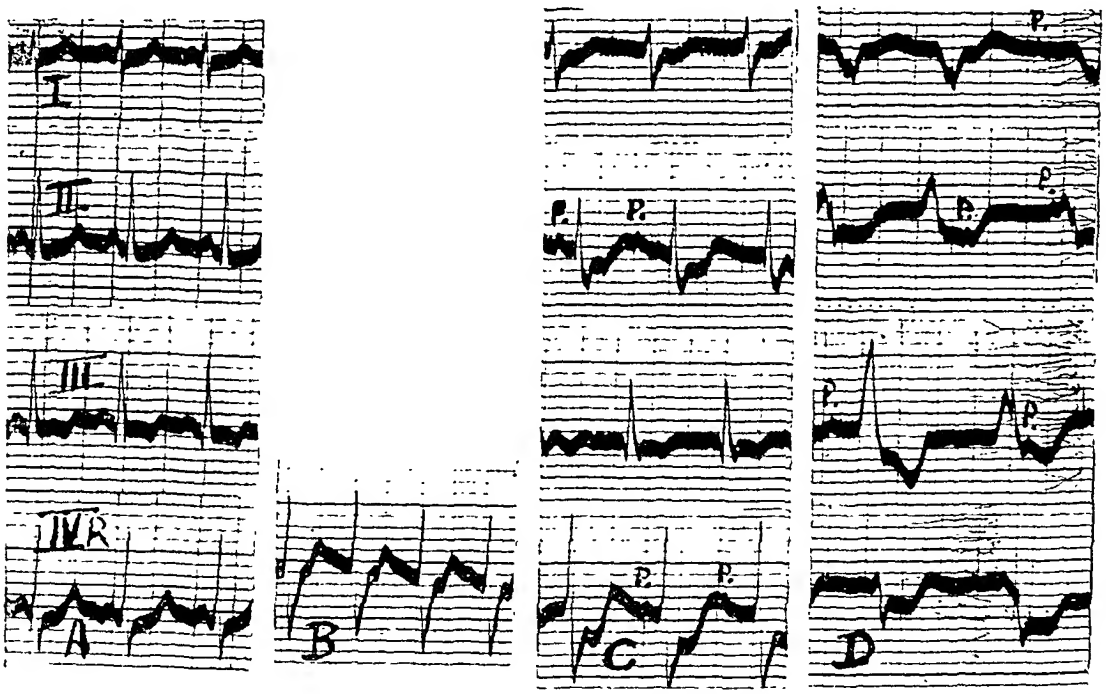

FIG. 7.—Case 8. Development of complete heart block and bundle branch block. (A) 4th day. (B) 6th day. (C) 8th day. (D) 9th day. See text.

EC. (Fig. 7D). C.H.B. with alternate ventricular extrasystoles; auricular rate about 126, ventricular rate about 90; R.B.B.Bl. Died 3 hours later.

Necropsy. Liver: some venous congestion, necrosis in centre of lobules; fatty degeneration. Lungs: congestion and small areas of collapse. Heart: weight, 110 g.; left ventricle, maximum thickness 12 mm., minimum 7 mm., pericardial and sub-endocardial petechial hæmorrhages; some plaques of atheroma in aorta just above aortic valve cusps, largest 3 by 5 mm.; on section, degeneration of muscle all chambers; areas of hæmorrhage into muscle; œdema slight; no cellular infiltration, no fibrosis.

Cases Simulating Bundle Branch Block

Case 9. J. P., age 8. Antitoxin given on 3rd day of disease. Diphtheria immunization 2 years previously. Mild tonsillar diphtheria; no abnormal cardiac signs; B.P. 100/50. 4th day: EC., N.R., rate 75; P–R, 0·18 sec., P diphasic. 13th day: EC., N.R., rate 85; P–R unchanged, P diphasic still, but increased in amplitude; T diphasic in leads II and III. 30th day: convalescent; no abnormal cardiac signs; EC. (Fig. 8), N.R., rate about 80; P diphasic; with sinus slowing "A-V nodal" escape beats appear with an upright QRS of 0·17 sec., depression of S–T and diphasic or positive T; in lead III a sinus rhythm only recorded; in lead II the fourth ventricular complex is preceded by a P wave with a P–R interval of 0·11 sec.; this QRS is intermediate in form between the QRS of the preceding "nodal" beats and the QRS of the following sinus beats; the last "nodal" beat in lead IVR is preceded by a negative P with a P–R interval of 0·11 sec. 32nd day: EC., N.R., rate 88; no sinus arrhythmia; and no "nodal" beats, otherwise tracing unchanged. Discharged well after 37 days in hospital. On re-examination 18 months later the child was quite well; no abnormal clinical signs; radioscopy: slight prominence of left middle arc; EC., N.R., rate 70; P–R, 0·18 sec., P of normal shape in limb leads, but diphasic still in IVR; ventricular complex physiological.

Case 10. C. T., age 10. Antitoxin on 4th day of illness; not immunized. Naso-pharyngeal diphtheria; severe toxæmia, bull-neck. 9th day: apex beat not palpable, sounds distant; EC. (Fig. 9), N.R., rate about 70; left axis deviation; S–T depression in lead I, T IV diphasic; in leads I and II the beats appear to originate in the A-V node, except for the last two beats in lead I and the last beat in lead II; in the "nodal" beats QRS is wide, S–T depressed, and T negative or diphasic, the pattern being similar to that seen in Case 9; in the last cycle but one in lead II QRS is preceded by a P wave with a P–R interval of 0·11 sec.; this QRS is intermediate in shape between the preceding "nodal"

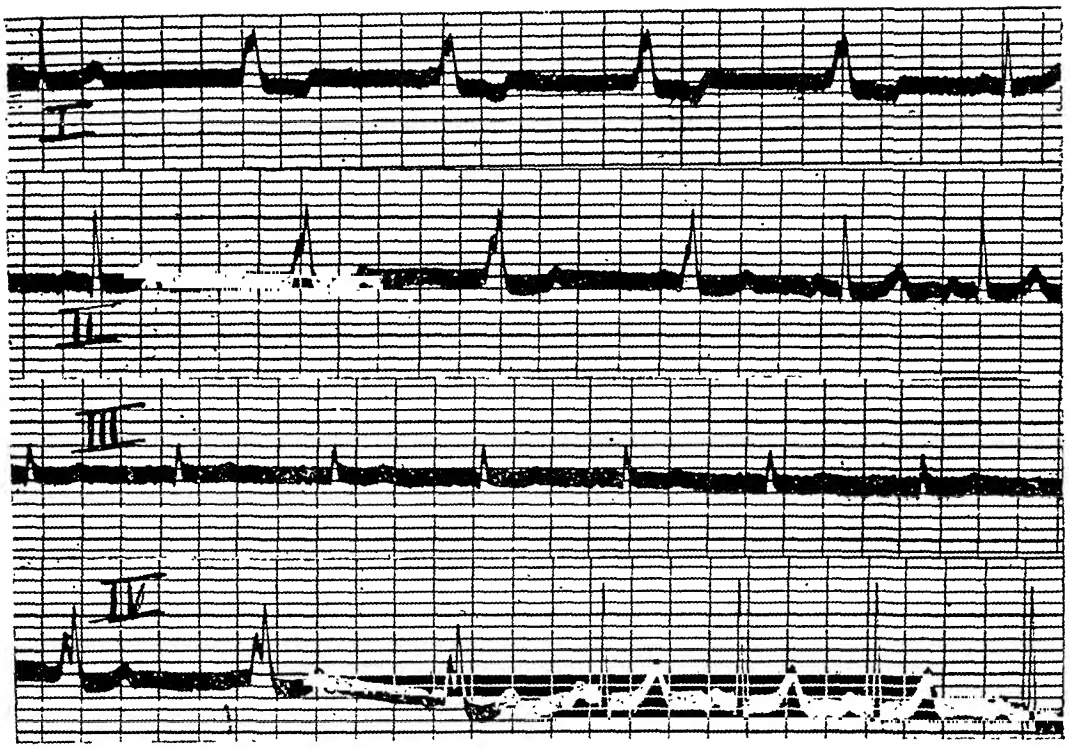

FIG. 8.—Case 9. Nodal escape beats simulating bundle branch block. See text.

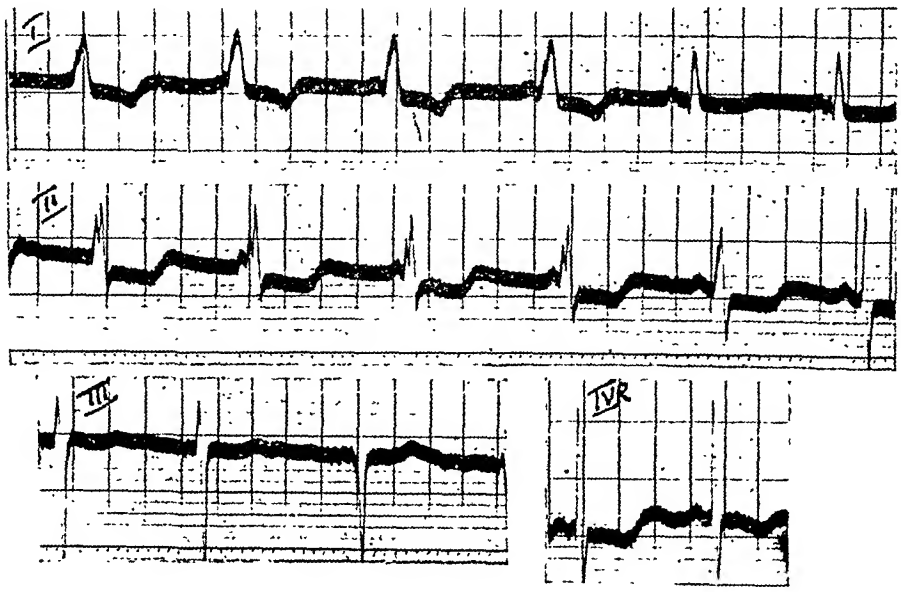

FIG. 9.—Case 10. 9th day. Nodal beats simulating bundle branch block. See text.

and succeeding sinus beat. 22nd day, palatal palsy and heavy albuminuria. 41st day: knee jerks absent, no abnormal cardiac signs; EC., N.R., rate 80, sinus arrhythmia; P–R, 0·12 sec.; T low voltage, and just negative in lead III. 53rd day, facial paralysis. 57th day: EC. N.R., rate 75; left axis deviation; T low voltage and just negative in lead III. Discharged from hospital on 124th day. On re-examination 7 months later, the child was quite well; no abnormal clinical or radioscopic signs; EC., normal rhythm, rate 70; left axis deviation, but QRS and T now of normal amplitude; and T III had become positive.

DISCUSSION

The histological studies in the four fatal cases show how intense are the degenerative changes in the myocardium in diphtheria and explain the variety of cardiographic changes recorded in the course of the disease.

Heart Block. An increase in conduction time between auricle and ventricle is not, as in rheumatic carditis one of the commonest manifestations of the myocardial injury, yet some interference with conduction was seen in all the cases with bundle branch or complete block (Cases 5–8) and there were in addition four cases in which an alteration in the P–R interval was the only indication of impaired conductivity .It is in the sub-acute phase of the disease, say after the eighth day, that a large proportion of cases show evidence of cardiac lesions and o systemic congestion, notably by an enlarged tender liver. At this time the heart rate is characteristically not increased and is often slow for a child; this relatively slow rate may conceal a defect in the conducting bundle which might be revealed at higher rates. The sinus bradycardia is another reason, in addition to the occurrence of high ventricular rates in complete block, why cardiography is essential for the diagnosis of block in diphtheria.

The single example of complete block in this series (Case 8) was found in an un-immunized girl aged 8, who had 36,000 of antitoxin intravenously and 40,000 units intramuscularly about 48 hours after the onset of symptoms. From the time of admission there was a progressive deterioration in the clinical condition, cardiograms showing S–T depression in all leads on the fourth day, increase in A-V conduction time and bundle branch block by the sixth day, and by the eighth day when she was vomiting blood and petechiæ were present in the skin, complete block with a ventricular rate of 115 was recorded. Before death on the tenth day the pulse had become slower and irregular due to complete block and alternate ventricular extrasystoles.

Bundle Branch Block. The records of this rhythm (Fig. 2–9), show that the pattern is not fixed but that rapid changes occur from day to day. A frank right bundle branch block picture was commoner than left, but low voltage, concordant, and " S " types and intermittent block were also seen. These quick changes suggest a rapidly extending lesion in the myocardium. But in Case 7 another factor behind these changes is seen, where the QRST pattern altered with the onset of nodal rhythm, both when this appeared spontaneously (Fig. 5), and when induced by an injection of atropine (Fig. 6B). This change may be compared with those to be discussed in connection with Cases 9 and 10. The usual discordant QRST pattern of bundle branch block shows reciprocal deviation of the S–T segment in leads I and III, but in most of the examples recorded here the S–T depression which is a characteristic and early change in toxic diphtheria is superimposed, resulting in S–T depression in all leads. A record from Case 6 taken in the terminal stage (Fig. 3C) does show reciprocal deviation of the S–T segment and is similar to that seen in acute cardiac infarction of posterior type. Studies of sections from this heart showed the most widespread degeneration to be in the posterior wall of the left ventricle with areas of almost complete necrosis.

Auricular Fibrillation and Auricular Flutter. Neither of these rhythms was encountered in any of the patients of this series.

Permanent Lesions. To establish the existence of permanent conducting lesions due to diphtheria it would seem necessary to have records showing the inception of the lesion during the disease. Such records are not always presented in published cases, but even so their number is few and it is generally accepted that however severe the lesions they clear up completely if the patient survives, and that to this rule exceptions are extremely rare. So far as branch block and complete block are concerned, no further light is thrown on this point by the cases reported here as all were fatal. But in one instance of latent block (Case 4) a prolonged P–R has persisted for five months, though the complication of chronic rheumatic carditis has to be taken into account. Moreover, persistence for five months is probably insufficient to classify a lesion as permanent.

Simulation of Bundle Branch Block. Two records were obtained (Cases 9 and 10, Fig. 8 and 9), showing abnormal ventricular complexes in beats arising in an ectopic focus, which at first sight suggest bundle branch block. In Case 10 they were discovered on the ninth day when the child was still seriously ill, but in the other on the thirtieth day when the patient was convalescent after a mild attack of the disease. In both instances QRS is wide enough to suggest bundle branch block, but the main deflections are upright and the increase in QRS is mainly due to prolongation of the proximal limb of R, the distal limb being little affected. Nor is the direction of T uniformly opposite to that of QRS. Apart from these considerations there is no reason, theoretically, why the function of a bundle branch should

be impaired during a short period of an ectopic rhythm, while it can conduct impulses from the sinus at a faster rate. In both tracings (Fig. 8 and 9) lead II shows a ventricular complex intermediate between that of nodal and sinus beats when it is preceded by a P wave, with a P–R interval of 0·11 sec. The R–T interval is increased by up to 0·03 sec., but not more.

These appearances have some similarity to the short P–R, wide QRS pattern, which has been described in particular by Wolff, Parkinson, and White (1930) and by Hunter, Papp, and Parkinson (1940), except that there is no constant relation between the P wave and the ventricular complex and that a passive ectopic rhythm is obviously involved. Many theories have been advanced to explain these complexes, but in the present instances a centre near the A-V node with rhythmicity greater than that of the node itself and from which impulses reach the ventricles by an unusual pathway seems most acceptable. An abnormal conducting path seems indicated by the occurrence of complexes of intermediate form when preceded at sufficient interval by a P wave. These presumably represent a fusion beat the result of two impulses one from the ectopic focus the other from the sinus, conducted along their own separate routes. Whatever view is accepted, however, the important point is that complexes of this type should not be held to represent a myocardial defect.

Summary

Clinical and cardiographic findings are given of 8 cases showing conduction changes among a series of 83 patients with diphtheria. Of 4 with latent block, a prolonged P–R interval has persisted in one for five months. Bundle branch block in 4 un-immunized children, aged 12 or less, and all died; and complete block was recorded in one of these four. In 2 others bizarre ventricular complexes were found in association with a passive ectopic rhythm; at first sight these suggest a bundle branch lesion: but like the short P–R, wide QRS syndrome, which seems a related condition, these changes do not appear to have any prognostic significance.

I have to thank William McNaughtan for his kind help with the histology; and George Chesney and Gordon Smith, Medical Officers of Health, for kindly allowing me to investigate patients in infectious diseases hospitals.

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ELECTROCARDIOGRAPHIC CHANGES AND THE EFFECT OF NIACIN THERAPY IN PELLAGRA

BY

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In a previous communication (Rachmilewitz and Braun, 1944), we reported on electrocardiographic changes in patients showing clinical signs of niacin (nicotinic acid) deficiency, which were eliminated by administration of this vitamin: we concluded that they were due to this specific deficiency. Our observations on the effect of niacin on these cardiographic changes have since been extended, and the results of these studies are now reported.

Present Investigation

Clinical and cardiographic studies were made on 27 patients suffering from pellagra. The outstanding clinical manifestations were those attributable to niacin deficiency such as pellagrous dermatitis, stomatitis, gastro-intestinal disturbances (most frequently diarrhœa), and mental symptoms. In 22 cases there were typical skin lesions of pellagra, varying in degree and intensity; in some the acute erythematous lesions were present, in others there was hyperkeratosis and pigmentation of the exposed parts of the body. In 3 cases no skin changes were present; 3 other patients had had typical pellagra dermatitis on previous occasions, but not at the time when the studies were made. In these 6 cases the diagnosis of the deficiency state was based on glossitis and on gastro-intestinal and mental disturbances. In addition to the diagnostic features of niacin deficiency, some cases of the entire group also exhibited signs of ariboflavinosis, such as, cheilosis, angular stomatitis, and corneal vascularization. In 10 of the cases there was also evidence of thiamin (B_1) avitaminosis consisting of pain in the calf muscles, para-æsthesia, muscular weakness, and cramps, as well as objective findings indicating peripheral neuritis and sometimes also pyramidal involvement.

No one of the cases included in this report had obvious disturbances of the cardiac function and no one was suffering from heart failure as seen in beriberi heart. When œdema of the lower extremities was present it was associated with hypoproteinæmia, but was obviously not due to cardiac insufficiency. The subjective complaints of the patients referable to the heart were insignificant; only a few patients experienced a feeling of oppression and palpitation. Corresponding to the poor general condition of the patients and the state of malnutrition, the blood pressure on admission was usually below normal, and increased gradually with the clinical improvement. There were no striking deviations in the pulse pressure. The pulse rate, before the specific treatment, varied from 37 to 110, ranging in most from 60 to 80, and scarcely changed after the specific treatment. In the few cases with a rapid pulse, it became slower after treatment. In one case a bradycardia of 37 beats a minute disappeared with recovery.

Clinical and X-ray examinations showed the heart to be normal or sometimes subnormal in size. In a small number of cases circulation time and venous pressure estimations were made and normal values were observed.

Cardiographic tracings were taken before treatment and at frequent intervals following various therapeutic procedures, consisting of individual vitamins of the B complex. Since we were concerned particularly with the differentiation of the effect of niacin from that of thiamin, a number of the cases were put on a vitamin B_1 poor diet, while receiving niacin, while in others vitamin B_1 was given during a certain control period before the institution of niacin treatment.

Group 1. *Cases with Prompt Response to Niacin*

This group comprises 16 patients, all with cardiographic changes of varying degrees and intensity before treatment. The age of these patients ranged from 16 to 65, the majority being below 50. The most striking changes were frequently seen in the younger patients, but the response to treatment was equally effective in the older patients. The cardiographic changes were manifested mainly on the final deflection: alterations of the S–T segment or of the T wave were present in all those with abnormal records. S–T depression in at least two limb leads was present in 9 cases; in 4 S–T was below the isoelectric line in one lead only. Abnormalities of the T wave in at least two leads were present in the entire group of cases; the T waves were negative, absent, diphasic, or flattened. In all except three, chest leads (CF) were taken. Out of these 13 records with chest leads 10 showed negative or flat T waves. The ventricular complexes, the P waves, and the P–R intervals were practically normal in all the records.

In all cases the response to niacin treatment was an improvement of the cardiogram. The positive effect was usually seen after 4–5 days of treatment, which consisted of niacin by mouth in daily doses of 300 to 500 mg. Only occasionally, in patients suffering from severe diarrhœa or vomiting, the peroral administration was supplemented by intravenous injections of 50 to 100 mg. daily. In most cases the optimal effect was obtained after 3 to 5 days and remained so after discontinuation of the medication. In some cases, however, the treatment had to be continued because of incomplete improvement and in these a normal curve was obtained after continuing the treatment for another 10 to 14 days. The cardiographic and clinical improvement were not always parallel, and a normal pattern was frequently obtained when the dermatitis and the changes in the mouth and gastrointestinal tract were still present.

The pathological character of the cardiogram disappeared usually simultaneously in all leads and the improvement was most striking where the changes had been the most prominent. The S–T depression disappeared and the T waves became positive or more elevated.

Table I shows the changes that took place as the result of the treatment. The degree

TABLE I

Case No.	Sex and Age	Pulse on admission	Electrocardiographic findings	
			Before treatment	After treatment
1	F. 30	80	T I absent, T II, T III, T IV negative, depression of S–T (II, III)	T I, T II upright, T III, T IV absent, S–T (II, III) isoelectric
2	M. 50	37	T I absent, T II, T III diphasic, depression of S–T (II, III)	T I, T II, T III, T IV upright, normal, S–T (II, III) isoelectric
3	M. 65	66	Extrasystoles, T I absent, T II, T III slightly negative, depression of S–T (II, III)	Sinus rhythm, T I absent, T II, T III positive, S–T (II, III), isoelectric
4	F. 25	110	T II flat, T III absent, depression of S–T (I, II, III)	T II upright +, T III absent, S–T (II, III) isoelectric
5	F. 50	80	T I, T II flat, depression of S–T (I, II, III)	T I upright +, S–T (I, II, III) isoelectric
6	F. 51	80	T I flat, T IV negative, depression of S–T (I, II, IV)	T II upright ++, T III upright ++, T IV positive
7	M. 50	85	T I, T II, T III, T IV flat, depression of S–T (II)	T II upright ++, T III upright ++, T IV upright ++, S–T (II) isoelectric
8	F. 45	60	T I, T II flat, T III negative, T IV diphasic	T I upright +, T II upright ++, T III positive, T IV upright ++
9	M. 50	58	T I absent, T II, T III flat, depression of S–T (II)	T I positive, T II upright +, S–T (II) isoelectric
10	F. 45	80	T I flat, diphasic, T III negative, TII, T IV flat, depression of S–T (I, II)	T I upright +, T II upright ++, T III positive, T IV upright +, S–T (I, II) isoelectric
11	M. 58	62	T I, T II, T III, T IV flat, S–T (I) above zero level, S–T (II) depressed	T I upright +, T II upright ++, T IV upright ++, S–T (I, II) isoelectric
12	M. 20	80	T I flat, diphasic, T II flat, T III, T IV absent, depression of S–T (I, II)	T I, T II, T IV upright +, S–T (I, II) isoelectric
13	F. 30	52	T I, T II flat, diphasic, T IV negative	T I upright +, T II upright ++, T IV negative
14	M. 26	80	T I absent, T II, T III flat, depression of S–T (II, III)	T I flat, T II upright ++, T III upright ++
15	F. 60	58	T I, T II, T III flat, T IV negative, S–T (II, III) elevated	T I upright +, T II upright ++, T III upright +, T IV positive, diphasic, S–T (II, III) elevated
16	M. 16	85	T I, T II, T IV flat, T III negative, depression of S–T (I)	T I upright +, T II upright +, T III negative, T IV upright ++, S–T (I) isoelectric

of elevation of the T waves following niacin administration was designated as + corresponding to an elevation of 0·5 mm. ± 0·25 mm.; as ++ corresponding to an elevation of 1 mm. ± 0·25.; and as +++ corresponding to an elevation of 1·5 mm. ± 0·25 mm.

The following are a few typical case histories.

Case 6. A woman of 51 was first seen in the out-patient department 18 months before her admission to hospital. She then had pellagrous dermatitis for which niacin was prescribed. She discontinued treatment because of a burning sensation in the skin following the intake of the drug. During this time she complained of general weakness and poor appetite, and mental disturbances appeared—irritability, depression, and defects of memory. A fortnight before admission, she started a temperature which continued for 10 days and was accompanied by diarrhœa. Subsequently her mental condition deteriorated rapidly and for this reason she was admitted on 8/12/42.

On admission she was disorientated, restless and confused, and there was no control of fæces and urine. Slight pellagrous changes were seen on the back of both hands. The tongue, lips, and gums were bright red and sore. In addition, angular stomatitis as well as seborrhœic accumulations in the naso-labial folds were present. The reflexes of the upper and lower extremities were exaggerated and there was a right patellar clonus and positive Babinski and Oppenheim on the same side.

Laboratory findings. Urine and stools, normal. Blood picture: Hb. 12·5 g.; red blood cells 3,600,000; white blood cells 7,600 with a normal differential count. Blood chemistry: urea 31·5 mg, sugar 92 mg., NaCl 598 mg., total protein 5·74 g., albumin 4·30 g., each per 100 c.c. Pyruvic acid in the urine 174 mg. The examination of the gastric juice after a caffeine test-meal and histamine injection revealed complete achylia.

Physical examination of the heart showed normal findings; pulse rate 80, blood pressure 110/90. Fig. 1A, taken on Dec. 9, showed a depressed S–T interval in the first, second, and fourth leads and a negative T wave in the fourth lead. Treatment with niacin was started on Dec. 9; 500 mg. by mouth and 50 mg. intravenously were given daily. After three days a marked change in the patient's mental condition took place. She became coherent, orientated, and began to eat. Control of urine and fæces was also regained. Four days after the start of treatment Fig. 1B showed improvement; S–T II became less depressed, the T waves in the three limb leads became more elevated and a positive T wave appeared in the fourth lead. After continuous treatment with niacin the spastic state of the extremities gradually improved and the clonus disappeared.

Case 7. A 50 year old man, of poor social condition, was brought to the hospital on 5/11/42, in a state of mental stupor which, according to information obtained from relatives, was of 5 days'

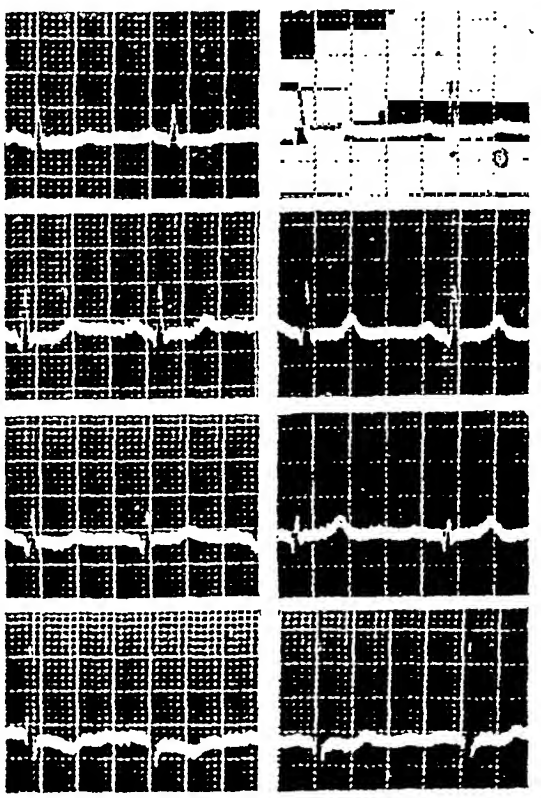


FIG. 1.—Case 6. (A) Before treatment. (B) After 4 days of niacin treatment.

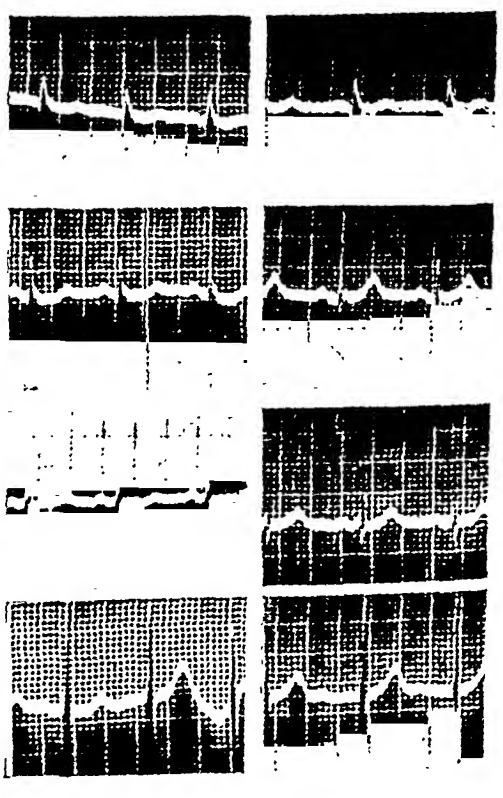


FIG. 2.—Case 7. (A) Before treatment. (B) After 5 days of niacin treatment.

duration. The acute illness was preceded by vomiting and severe diarrhœa persisting during 3 weeks. The patient, on admission, was incoherent, and there was no control of urine and fæcès. There was marked emaciation and slight œdema of the lower extremities; no evidence of pellagra dermatitis was present, except for slight hyperkeratosis with pigmentation on the back of the feet and hands. The patient exhibited signs of stomatitis and cheilosis. The reflexes of the lower extremities were decreased.

Laboratory findings. Urine: trace of albumin, a number of pus cells in the sediment, and the culture positive for *Staph. aureus*. The stool contained ova of ascaris. Blood picture: Hb. 70 per cent; red blood cells 2,700,000; white blood cells 8,400 with a normal differential count. Blood urea 35 mg., NaCl 650 mg., sugar 86 mg., total protein 5·76 g., albumin 3·8 g., vitamin C 0·4 mg., each per 100 c.c. Pyruvic acid in the urine 153 mg.

The clinical examination revealed normal findings in the heart, which was not enlarged. Pulse rate 85, blood pressure 105/70. Fig. 2A, taken immediately after admission, and also 24 hours later after parenteral administration of 2 litres of physiological saline solution, showed S–T depression in the second lead and low positive T waves in all leads. From November 6 to 11, niacin was given, 500 mg. daily by mouth and 100 mg. intramuscularly. Two days after beginning of treatment the mental state began to clear up, the patient began to eat and regained control of urine and fæces. This improvement continued during the following days. Fig. 2B, taken November 11, showed S–T II isoelectric and marked elevation of T II, T III, and T IV.

Case 8. A 45 year old woman, with a history of chronic amœbiasis and repeated attacks of diarrhœa, especially during the hot summer months. The first appearance of pellagra dermatitis was noted three years ago. Since then, each attack of diarrhœa was followed by a burning sensation in the tongue and lips as well as by dermatitis on the back of both hands. On 22/7/43, the patient was admitted to hospital, presenting clinical symptoms of pellagra of two months' duration. There were digestive disturbances and psychic changes. The patient also complained of pain in the arms and legs, but no abnormal neurological findings were obtained. No œdema was noted.

Laboratory findings. The stool contained *Entamœba histolytica.* The gastric juice analysis showed complete absence of free hydrochloric acid following caffeine by mouth and histamine injection. The blood picture : Hb. 9·25; red blood cells 3,600,000. Blood chemistry: urea 21 mg., sugar 81 mg., ascorbic acid 0·6 mg., each per 100 c.c. Pyruvic acid in the urine 190 mg.

The clinical findings of the heart were essentially normal and there were no signs of heart failure; the pulse rate was 60 and the B.P. 115/70. A cardiogram, taken on July 24, showed low positive T waves in leads I and II, T III inverted and T IV diphasic. After three days of niacin medication consisting of daily doses of 350 mg., the clinical signs of deficiency began to clear up. A cardiogram, taken on July 27 showed marked elevation T I, T II, the negative T III became slightly positive; the most striking improvement, however, took place in T IV which became high and upright. The same pattern was obtained after continuing treatment with niacin for another week.

Group II. Cases with Delayed Response to Niacin

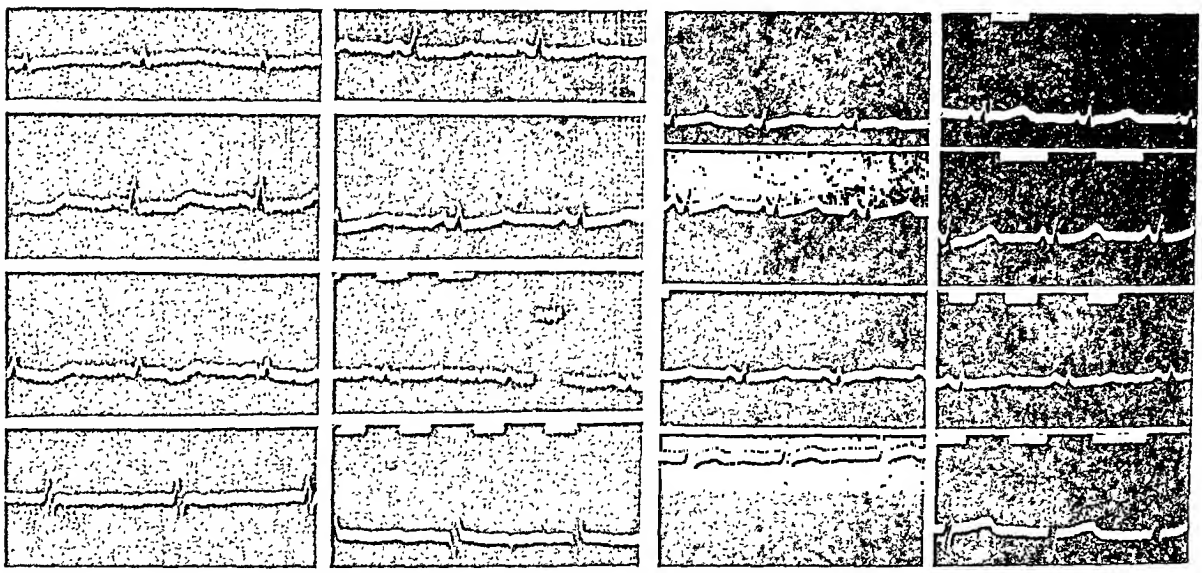
In this group, consisting of two patients suffering from severe deficiency of the vitamin B complex, the immediate improvement in the clinical symptoms and in the altered cardiogram following administration of niacin was slight or absent. In addition to the vitamin B deficiency these patients had also appreciable œdema of the lower extremities and ascites due to severe hypoproteinæmia and hypoalbuminæmia.

In the course of treatment the improved absorption and utilization of food in one case and plasma infusion in the second case resulted in a rise of the blood proteins and disappearance of the œdema. Niacin was again administered and was followed by a noticeable improvement of the cardiogram. These cases will be described briefly.

Case 17. A 40 year old woman suffering from repeated attacks of diarrhœa and chronic malnutrition was admitted on 10/12/43 in an extremely poor condition. She was highly emaciated and showed œdema of the lower extremities. The clinical symptoms of vitamin B deficiency were the following: mental deterioration with incontinence of urine and fæces; typical pellagrous dermatitis on the dorsum of both hands, atrophic glossitis, and severe diarrhœa; in addition there were neuritic manifestations, consisting of hyperreflexia and a positive Babinski reflex on the right side. Thus there was evidence of both niacin and thiamin deficiency. Laboratory examinations revealed a moderate degree of normocytic anæmia and marked hypoproteinæmia with hypoalbuminæia (total protein 4·7 g., albumin 1·93 g., each per 100 c.c.

The heart was normal in size with no evidence of failure. There was no pulmonary congestion and no hepatic engorgement. The pulse rate was 60, the blood pressure 105/65. Fig. 3A, taken on admission, December 10, showed marked abnormalities in all leads, low voltage of the QRS complexes, S–T II and S–T III noticeably depressed, T I and T IV absent, T II and T III low positive. During the following six days the patient was given a diet which contained only 0·5 mg. vitamin B_1; to this was added niacin 500 mg. by mouth and 100 mg. intramuscularly daily. This resulted in

some improvement of the dermatitis and the mental state. The diarrhœa, however, was hardly influenced. Fig. 4B, taken on December 16, showed slight improvement: a small T wave appeared in the first lead and the S–T depression in leads II and III disappeared. Niacin was then discontinued and for the following twelve days vitamin B_1 was given, 30 mg. daily intramuscularly. At the end of this period no improvement of the clinical condition was noted and the degree of the œdema remained the same. A cardiogram taken on December 28 was practically the same as before. The following fortnight, although no specific treatment was given, was characterized by gradual and steady clinical improvement of the patient and a marked increase in diuresis, which finally resulted in complete loss of the œdema. The subsidence of the diarrhœa and improved absorption of food resulted in an increase of the serum proteins to 6·5. Fig. 3C, taken on January 10, showed slight elevation of the T waves in all leads, the voltage of the QRS complex remaining the same. During the following six days niacin was given again, the daily medication consisting of 500 mg. by mouth



A B C D

FIG. 3.—Case 17. (A) Before treatment. (B) After 6 days of niacin treatment. (C) A fortnight later, after general improvement and increase in serum proteins. (D) After a second course of niacin treatment during 6 days.

and 100 mg. intramuscularly. Fig. 3D, on January 16, showed further improvement of the T waves in all four leads without changes in the voltage of the QRS complexes.

In this case, which was characterized by niacin and B_1 deficiency and by marked œdema due to hypoproteinæmia, the first trial with niacin produced only slight improvement of the cardiographic pattern; the administration of B_1 had no effect. With the gradual amelioration of the general condition of the patient together with better utilization of food, loss of the œdema, and rise in serum proteins there was a gradual improvement. At this last stage, a short course of niacin caused additional improvement of the cardiogram.

Similar observations were made in *Case* 18. This was a woman, 30 year old, who had been under treatment in hospital several times during the last three years because of severe pellagra precipitated by excerbations of chronic purulent sinusitis. On last admission, 13/7/43, the patient had fever and severe diarrhœa. The outstanding findings at this time were œdema of the lower extremities and ascites, severe atrophic glossitis, and mental changes. The heart was not enlarged on clinical and fluoroscopic examination; the contractions, however, were feeble. There was no distension of the cervical veins and the liver was not enlarged. The pulse rate was 65, B.P. 120/80. The stools contained cysts of *Entamœba histolytica*. The blood picture showed a moderate degree of hypochromic anæmia; blood proteins 3·7 g., albumin 1·3 g., per 100 c.c. Fig. 4A, 13/7/43, showed marked abnormalities especially of the final deflections of all leads. The first trial with niacin (7 days 500 mg. orally and 100 mg. intramuscularly), did not produce appreciable changes in the clinical state of the patient, the œdema rather increased during this period. Fig. 4B, taken on July 21, showed further deterioration, the T waves in the second and third leads becoming slightly negative.

Between July 21 and July 27, only vitamin B_1 was given, 40 mg. daily intramuscularly. This treatment had no effect on the œdema, the diarrhœa, or the cardiogram. On July 30, a plasma infusion of 400 c.c. was given. Since that date an increase in diuresis took place; this was accompanied by gradual but steady diminution of œdema and ascites. At the same time the diarrhœa markedly diminished in severity and the patient began to eat, the diet containing 70 g. animal proteins per day. On August 7, the total proteins were 5·7 g. and the albumin 3·3 g. per 100 c.c. At this time, another tracing was taken which still showed severe pathological changes. The voltage of the

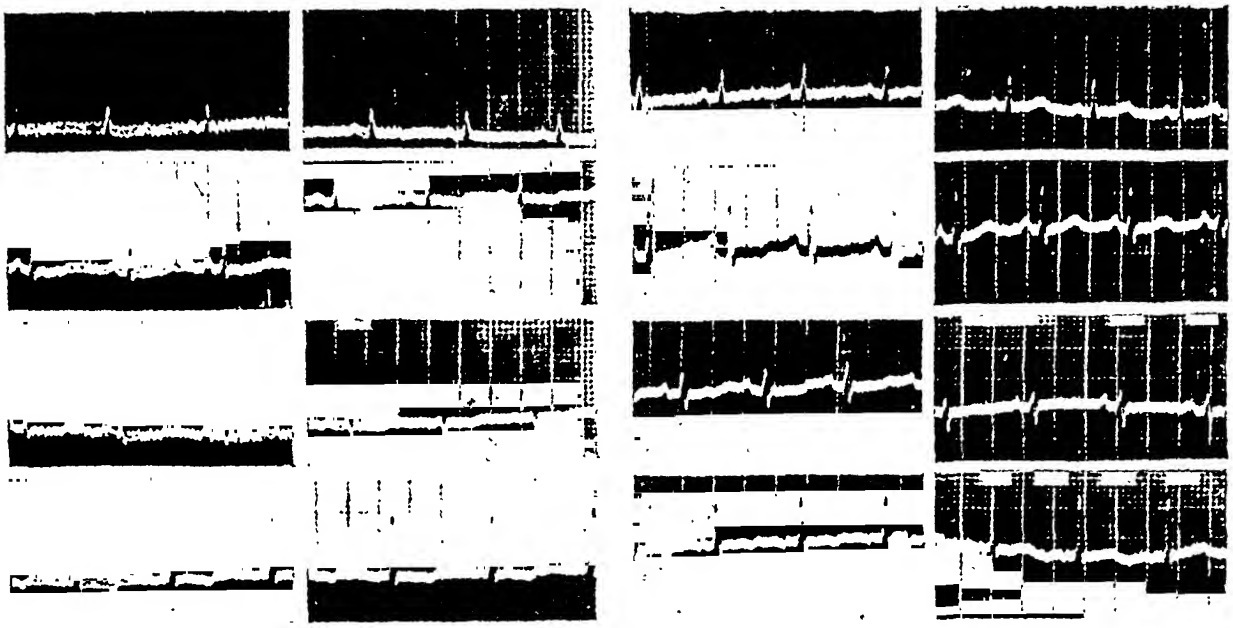


FIG. 4.—Case 18. (A) Before treatment. (B) After 7 days of niacin treatment (first trial). (C) After thiamin treatment and plasma infusion. (D) After 5 days of niacin treatment (second trial).

QRS complexes, however, increased (Fig. 4C). The last trial with niacin (5 days of 300 mg. by mouth daily) was followed by striking improvement of the cardiogram, which became practically normal (Fig. 4D).

Group III. Cases of Pellagra with no Alterations of the Electrocardiogram

In the third group comprising 9 cases, the original cardiographic changes were very slight or entirely absent, although the age incidence in this group was even higher than in the first group. Analysing the clinical symptomatology of these patients, it became evident that the outstanding sign was the pellagrous dermatitis, the visceral deficiency manifestations being either very slight or entirely absent. All these patients were ambulatory and visited the out-patient department because of the skin changes. Some of them complained of burning sensation in the tongue and lips. It seems thus that the heart in pellagra is affected mainly in cases in which other visceral organs, such as the brain, stomach, and intestines, show clinical evidence of involvement. When skin changes alone are present in pellagra alterations in the cardiogram may not occur.

COMMENT

The only vitamin deficiency known to be associated with cardiovascular disturbances is that of vitamin B_1, e.g. beriberi heart disease which is manifested by cardiac enlargement and heart failure. Experimental as well as clinical B_1 avitaminosis is associated with cardiographic changes which disappear following B_1 administration. The electrocardiogram was also found frequently changed in pellagra. Since in deficiency diseases in man several factors of the vitamin B complex may be lacking simultaneously, the presence of cardiographic changes in pellagra was attributed to B_1. Feil (1936) in a study of 38 cases of pellagra found 19 with abnormal cardiograms, chiefly concerning the final deflection of the ventricular complex; in some instances, they returned to normal with recovery. The conclusion drawn by this author was that pellagra and beriberi apparently affect the heart physiologically in much the same way. Porter and Higginbotham (1937), on the other hand, found no characteristic changes in endemic pellagra and concluded that beriberi and pellagra have no comparable effect on the heart.

The above-mentioned observations were made before the introduction of niacin in the treatment of pellagra.

Mainzer and Krause (1940), found a high incidence of abnormal cardiograms in pellagrins in Egypt, but believed that these changes were not characteristic of pellagra and that their occurrence was not sufficient to warrant the conclusion that they were caused by a deficiency of niacin. However, they noticed that there was a parallelism between the course of the disease and the cardiographic changes, and that these disappeared rapidly in some cases following niacin therapy. In the first case report of pellagra successfully treated with niacin, Smith, Ruffin, and Smith, (1937) found low upright T waves in all leads; on the seventh day of treatment the T waves had returned to normal.

The cardiac manifestations in pellagra obviously differ from those in beriberi. Observations reported by others as well as by ourselves clearly show that the heart in pellagra is not enlarged; its size is normal or frequently subnormal. Obvious disturbances of cardiac function and heart failure have not been found in pellagra as is the case in beriberi heart. In our cases of pellagra with œdema of the lower extremities and ascites there was no evidence of congestive heart failure, the œdema being explained by marked hypoproteinæmia. Vitamin B_1 had no effect on diuresis in these cases; only the rise in serum proteins was accompanied by an increase of diuresis and disappearance of the œdema.

It remained, however, to be shown that the cardiographic changes in pellagra are not due to deficiency of vitamin B_1. During recent years it has become possible by therapeutic tests with pure vitamins to separate the various symptoms and signs of most of the specific avitaminoses constituting the syndrome of pellagra. In order to eliminate the action of B_1, some of our cases were put on a vitamin B_1 poor diet while receiving niacin. In other cases vitamin B_1 was given first to establish whether this vitamin had any effect on the clinical condition and on the cardiographic changes. It was thus found that only the administration of niacin resulted in most cases in prompt and striking improvement of the clinical symptoms as well as of the cardiographic changes, showing that these changes in pellagra are due specifically to niacin deficiency.

Our observations seem also to indicate that there is a parallelism between the cardiographic abnormalities and the visceral manifestations of the disease. The most striking changes were seen in patients having lesions in the mouth and mental and gastro-intestinal disturbances, sometimes in the absence of dermatitis. On the other hand, the presence of skin lesions alone in chronic pellagrins without obvious involvement of the visceral organs may be associated with normal cardiograms.

The lack of immediate response to niacin in the two cases in which pellagra was associated with severe hypoproteinæmia is of special interest. In these cases the administration of niacin at first had no effect, either on the clinical signs of pellagra or on the cardiographic changes. A positive effect on both was seen only after restoration of the blood proteins. This lack of response to the specific treatment, as long as hypoproteinæmia existed, suggests that in these cases the hypoproteinæmia interfered with the utilization of niacin. Evidence of an interrelationship between protein intake and niacin utilization was given in the experiments of Sarett *et al.* (1942), who showed that in dogs there was an inverse relationship between protein intake and niacin excretion. The state of the liver in hypoproteinæmia might be responsible for the lack of utilization of niacin. Evidence of liver damage due to protein depletion in dogs was given by Elman and Heifetz (1941), who showed that the liver cells in these animals become vacuolated and that nearly all of the stainable cytoplasm becomes transparent. It may be assumed that in our cases disturbances of liver function during the state of hypoproteinæmia and hypoalbuminæmia were responsible for the failure of response to niacin. That liver damage actually existed was proved in one of these cases by means of the hippuric acid test. There was at the beginning no excretion of hippuric acid after intravenous administration of 2·0 g. of sodium benzoate. With the restoration of proteins, the excretion rose gradually to 0·65 g., which is practically normal.

The cardiographic abnormalities in pellagra, consisting mainly in alteration of the final deflection of the ventricular complex, are in themselves not specific and their presence does not necessarily indicate pellagra as the cause. Similar changes may occur in beriberi and in organic heart disease, most frequently in arteriosclerotic coronary artery disease. Only the fact that in pellagra these changes are reversible and disappear or improve after niacin admin-

istration, proves conclusively that they are caused by niacin deficiency and hence are a part of the pellagra syndrome.

The question naturally arose whether treatment with niacin has a similar effect on the cardiographic changes accompanying organic heart disease; particularly since observations were reported recently that niacin had a beneficial effect on pain in angina pectoris (Neuwahl 1942). In order to clarify this question six patients suffering from arteriosclerotic heart disease were selected. These patients showed depression of the S–T segment and flattening or inversion of the T wave in at least two limb leads. There was no history of recent cardiac events to account for these changes. These patients were given niacin for a period of 8 to 10 days and this medication had no effect whatsoever on the cardiograms.

The changes seen in pellagra can also resemble those present in myxœdema, namely flattening or absence of the T waves, and lowering of the voltage of the ventricular complexes. Even the heart rate in pellagra may occasionally be as low as in myxœdema. The myxœdema heart and the abnormal curves in this disease are known to be specifically affected by the administration of thyroid extract. There was, however, a possibility that niacin might also improve the pattern in myxœdema by influencing the metabolism of the heart muscle or by improving the circulation in the heart. Three cases of myxœdema with low basal metabolic rates and characteristic cardiographic changes were given niacin during 6 to 8 days before thyroid treatment. In all these cases niacin in the usual doses had no effect on the curves, which became normal only after thyroid medication.

The specific action of niacin on the cardiogram in pellagra could be explained in the first place by its effect on the coronary circulation. Niacin is known to produce vasodilatation of the skin as indicated by increased temperature and flushing in various parts of the body after administration of the drug. It is doubtful, however, whether the blood vessels of the visceral organs are at all affected by niacin. Investigations (Lomann *et al.*, 1941) have shown that the blood flow through the brain is hardly increased by this substance, although the pial vessels were found to be dilated (Moore, 1940). Furthermore, the vasodilatory action of niacin is transient in character; flushing of the skin usually disappeared within half an hour. According to the studies of Bean and Spies (1940) and our own observations, niacin has no immediate effect on the cardiogram. In several of our cases of pellagra cardiograms were taken before and immediately after the intravenous administration of 50 mg. of niacin and no reversal of the pathological changes was noted. The mode of action of niacin on the heart can hardly therefore be sought in its vasodilatatory effect on the coronary vessels. It seems more likely that the influence of niacin on the electrocardiographic changes in pellagra is due to some more fundamental action.

Cardiographic changes due to niacin deficiency are mainly manifested by alterations of the S–T segment and the T wave. Inasmuch as metabolic changes in the heart muscle are reflected in the T wave (anoxemia, thyroid deficiency, and avitaminosis B_1), any factor affecting the metabolism of the heart muscle may also affect the character of the T wave. According to McLeod (1938), the prolongation of the recovery period of cardiac muscle with a delay in the oxydation of the products of metabolism, is one of the factors responsible for the lowering of the T wave. It is suggested, that the changes in the T waves produced by niacin deficiency may also be of metabolic origin. Niacin is the chemically active fraction of the coenzymes which are essential for the intermediate metabolism of carbohydrates. Axelrod, Spies, and Elvehjem (1941) found a marked diminution of coenzyme I in the striated muscle of human subjects, deficient in niacin, and assumed that the coenzyme content may affect the ability of the human muscle to carry out its oxidative function. It seems logical, therefore, that the coenzyme deficiency also results in an altered metabolic state of the heart muscle. This view is further supported by the fact that the changes are reversible, i.e. they disappear after the administration of niacin.

Summary

The effect of niacin therapy on the cardiographic changes in 27 patients suffering from pellagra was studied. In 16 of them, with pronounced visceral manifestations of the disease, the response to niacin was prompt; the cardiogram improved or returned to normal after

several days of treatment. In some cases thiamin was given without any effect; these cases responded promptly to subsequent niacin treatment. In two cases complicated by severe hypoproteinæmia, the response to the first trial with niacin was slight or absent. Only after restoration of blood proteins was the effect of niacin on the cardiographic changes observed. In 9 cases which only had skin lesions no cardiographic abnormalities were found and no changes followed treatment.

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BLOOD VOLUME DETERMINATIONS WITH RADIOACTIVE PHOSPHORUS

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In experiments on animals, Smith, Arnold, and Whipple (1921) compared the three then known methods for determining the circulating blood volume, namely, the Welcher method, the carbonic oxide method, and the dye method. They recommended the method worked out by Dawson, Evans, and Whipple (1920), the so-called " blue azo dye T 1824 " method, for determinations of plasma volume. Gibson and Evans (1937) modified this method and with their co-workers applied it to a comprehensive series of clinical problems. There is no doubt that, thanks to these activities, plasma volume determinations have been aided by valuable experiences, but for studies of the circulating blood volume every method used, even the last-mentioned, lacks to a certain extent the prerequisites needed for completely reliable values. For example, when determinations of the plasma volumes are made by the " blue azo dye " method, the dye substance introduced is not taken up solely by the circulating blood but, as Gibson himself admits, is also taken up by, *inter alia*, the reticulo-endothelial system. Cardozo (1940), who made a special study of the passing of T 1824 into the lymphatic system in dogs, comes to the following conclusion: " The passing of the dye to the lymph interferes with a correct interpretation of a disappearance curve according to Gibson and Evans, and it usually results in the calculation of too large plasma volumes." Between 15 to 30 minutes after the injection of the dye substance into the blood stream the lymph assumed a blue colour and after two hours reached a concentration up to 49 per cent of that in the plasma.

It has been shown in previous works (Nylin, 1944 and 1945), by employing the method of Hahn and Hevesy (1940 and 1942) for labelling the red blood corpuscles with radioactive phosphorus, that in normal cases mixing and equilibrium between the injected labelled blood corpuslces and the blood stream are attained remarkably early—a contrast to the dye method. Gibson showed that " mixing time " does not set in until after 15 minutes in the special case, and on an average after 7·5 minutes for 15 normal subjects. The continuation of the curve Gibson calls the " disappearance slope," and he states that only relative constancy is attained in that the curve in its further course falls slowly towards the abscissa. It seems as though Hevesy's method affords the possibility of studying a number of circulation problems that had not been possible previously, because the fundamental prerequisite appears to have been satisfied, when it is possible to inject the subject's own blood corpuscles labelled with P^{32} which are continuously confined to the circulating blood for a relatively long time, and whose activity comes into equilibrium with the circulating blood remarkably early. Hevesy, Warburg, *et al.* (1944) made determinations of the circulating blood volume in normals both by Hevesy's and Hahn's methods with radioactive phosphorus and by the CO method and also by the dye method. As was expected, with the labelled blood corpuscles they obtained lower and, very probably, more reliable values than by the other methods.

In the present work Hevesy's method has been employed on clinical cases, it being of importance by means of fractioned specimens, preferably from arterial blood, to obtain a knowledge of " the dilution curve," and particularly in determinations of the amount of blood in dilated hearts, where the amount of residual blood has proved to have a great influence on the type of curve (Nylin, 1945). Not until one knows the course of the individual dilution curve can one indicate more closely where mixing and equilibrium take place and subsequently select the points, preferably the mean value of several specimens, which are to be the basis for the calculation of the circulating blood volume.

Methods and Results

In the present work the same method has been employed as in those previously published by the writer. For determinations of the circulating blood volume the activity was established, by means

of a Geiger counter, for the injected labelled blood corpuscles, and then for the fractioned specimens taken from the arterial blood. The calculation of the amount of circulating red blood corpuscles was made with the formula $x = A \times B$, where x indicates the amount of circulating blood corpuscles required in c.c., A, the amount of labelled blood corpuscles injected, and B, the relation between the specific activity of the labelled blood corpuscles injected and the specific activity of the blood specimens taken. The specific activity of the latter constitutes the mean value for a series of specimens after equilibrium had been attained, each value including 3–18 separate determinations in a single case. With the guidance of the hematocrit and the amount of blood corpuscles, the amount of plasma was calculated. Finally, the total of the amounts of plasma and blood corpuscles gives the circulating blood volume. In calculating the amount of blood corpuscles expressed in grams a specific gravity of 1·08, as used by Hevesy, has been taken.

The material comprises six subjects with normal hearts, six heart cases with varying ætiologies, and one case of anæmia; all were without signs of failure and had normal venous pressures. In addition there are two cases of typical cardiac failure, Case 14 with mitral stenosis and Case 15 with cardiosclerosis. The former had a venous pressure of 29 cm., the latter one of 17 cm. Both had much dilated hearts, as appears from their large heart volumes (see Table I).

For most cases detailed dilution curves have been published in an earlier work (Nylin, 1945). Among the normal cases, equilibrium between the injected activity and the circulating blood is attained already in the first minute in Case 1, and in the second and third minutes in the others. Case 2 was not subjected to a closer analysis of the dilution, but the specimens were taken as late as after the fifteenth minute. As emerges from Table I, the mean value for the amount of blood corpuscles for these seven normal cases is 1850 c.c., or 1998 g. per kilogram of body weight: these normal cases have a weight of circulating blood corpuscles of 33·4 g., somewhat less than that found by Hevesy *et al.*, which was 36 g. Nevertheless, the present material is so small that in this respect a comparison can hardly be made, but in each case the determination of the circulating blood volume is based, firstly, on a knowledge of the dilution curve in that individual case, and thus on a knowledge of when equilibrium was attained, and secondly on the mean value of a number of determinations on the same case.

In the group of compensated heart cases there is only one (Case 7), where equilibrium appears to be attained strikingly soon, in spite of the fact that the amount of residual blood in the heart would seem to be considerable. The heart volume is no less than 820 c.c./m.^{2} Repeated determinations with both decholin and with corpuscles labelled with radioactive phosphorus on the same patient showed remarkably short circulation times, which in this exceptional case could not be fully explained, though the possibility of a septal defect is not excluded. In the other cases in the last-mentioned group equilibrium set in later than in the normal cases, as appears from Table I; this conforms with the course of the dilution curve and the large heart volumes, which has also been pointed out in an earlier work (Nylin, 1945).

The circulating blood corpuscle volume in compensated heart cases, expressed in c.c., grams, or grams per kilogram of body weight, and the total amount of circulating blood do not diverge from the normal value but exhibit striking agreement with them. In these heart cases, too, the blood volumes given for the individual case are the mean values of a number of observations.

Of particular interest is Case 8, with a very large heart, 1230 c.c./m^2, where equilibrium appears to have been attained ten minutes after the injection of the labelled blood corpuscles. Four observations, made between 10 and 15 minutes after the injection, give a mean value of the amount of circulating blood corpuscles of 1275 c.c. The mean value of 8 observations 15–22 minutes after the injection is 1368 c.c. At the later determination an increase of 7·3 per cent in the circulating blood volume was obtained; that was probably due to the error of the method, which according to Hevesy *et al.* probably amounts to about 5 per cent. It is not out of the question that to some extent the increase may be due to the fact that as late as after the twenty-second minute, the activity had decreased somewhat and thus a somewhat too high figure for the amount of circulating blood corpuscles was indicated. We do not yet know with certainty how long the activity in the circulating blood remains constant.

The two with heart failure (Cases 14 and 15) have been subjected to detailed studies, and their dilution curves were published (Nylin, 1945). In spite of the considerable dilatation of the heart, probably with large amounts of residual blood, equilibrium nevertheless appears relatively early—from the second to the third minute. The amount of circulating blood corpuscles in Case 14 is as high as 46 g. per kilogram, and in Case 15 is 36 g. The total blood volume approaches twice the normal in Case 14, amounting to 6616 c.c. or 114 c.c. per kilogram of body weight. Remarkably enough Case 15 has neither so large an amount of blood corpuscles nor so great total blood volume, in spite of a pronounced insufficiency on May 15, 1944. Ten days later, when all the symptoms of failure had receded, the œdema disappeared, and the body weight decreased by 12 kg., both the

TABLE I

CIRCULATING BLOOD VOLUME IN NORMAL AND CARDIAC CASES

Case No.	Diagnosis	Date	Weight Kg.	Heart volume		Venous pressure cm.	Circul. time (decholin) sec.	Hb.	Red cells	Hematocrit	Injected labelled corpuscles g.	Specific activity of injected corpuscles (10^6 omitted)	Mean specific activity of samples	Red corpuscles			Plasma volume ml.	Total blood volume		Time for samples after injection (minutes)	Number of samples
				c.c.	c.c./m²									c.c.	g.	g./kg.		c.c.	ml./kg.		
1	Normal	2/7/43	65	520	310	12	10–17–22	91	4·9	45	1·23	0·233	120	2213	2390	36·8	2705	4918	75·5	1–1·5	10
2	,,	8/11/43	47				?	64	4·4	38	1·07	0·179	107	1657	1789	38·0	2714	4371	93	15–20	7
3	,,	28/1/44	69				?			48	1·36	0·373	245	1919	2073	30·0	2079	3998	57·9	3–8	4
4	,,	8/2/44	75	978	501	12	17–27–42	88	5·0	45	1·23	0·1435	85	1922	2076	27·7	2346	4268	56·9	3–15	15
5	,,	28/2/44	63	575	340	9	9–19–24	78	4·4	40	1·10	0·196	148	1352	1460	23·2	2028	3380	53·7	2–9	16
6	,,	19/4/44	49				?	75	4·0	39	1·13	0·388	200	2037	2200	44·8	3056	5093	103·9	3–10	12
	Mean									42·5				1850	1998	33·4	2488	4338	73·5		
	Compensated heart cases																				
7	Aortic regurgitation?	25/5/43	72	1460	820	14	17–27–30	76	4·9	46	1·26	0·2297	14	1920	2074	28·8	2253	4173	58·0	0·5–1	18
8	Aortic regurgitation	30/3/44	46	1720	1230	10	17–30–56	68	4·2	40	0·87	0·093	59	1275	1377	30·0	1913	3188	69·3	10–15	4
	,, ,,	,,									,,	,,	55	(1368)	(1477)	(32·1)	(2052)	(3420)	(74·4)	15–22	8
9	Hypertension	16/3/44	67	2100	1200	13	37–67–85	90	4·7	43	1·20	0·135	70	2140	2311	34·5	2830	4970	74·2	5–10	3
0	Cardiosclerosis	29/6/43	52	1480	830	5	32–57–83	92	5·0	54	1·55	0·229	162	2037	2200	42·3	1735	3772	72·5	2–4·5	8
	Constrictio cordis op.	12/6/44	65	821	470	10	13–20–29	76	4·5	41	1·23	0·095	59	1836	1983	30·6	2535	4371	67·2	5–19	8
	Acute polyarthritis and endocarditis.	19/4/44	84	1005	480	?	?	72	4·3	38·5	0·97	0·229	102	2020	2182	26·0	3160	5180	61·7	3–5	5
	mia	22/3/44	48					64	3·0	35	0·97	0·314	211	1339	1446	30·1	2487	3826	79·7	3–6	4
	Mean									42·5				1795	1939	31·8	2416	4211	71·8		
	Decompensated heart cases																				
14	Mitral stenosis	23/8/43	58	2038	1235	29	60–85–95	67	4·2	38	1·07	0·645	257	2481	2680	46·2	4135	6616	114·0	2–5	10
15	Cardiosclerosis	15/5/44	62	1613	895	17	35–52–65	78	4·1	46	1·26	0·0918	52	2064	2230	36·0	2423	4487	72·4	3–13	8
	After treatment compared.	25/5/44	50	1352	845	5	20–37–47	96	5·1	52	1·46	0·11	88	1687	1822	36·4	1557	3244	64·9	3–11	5

amount of blood corpuscles and the total blood volume had decreased, the latter by no less than 28 per cent, naturally owing to the disappearance of the fluid. It is remarkable on the other hand that the amount of blood corpuscles decreased by no less than 18 per cent—perhaps to accumulate in certain depots—in spite of the fact that both the hæmoglobin and the number of red blood corpuscles increased considerably.

Summary

By the application of a new method worked out by Hevesy and his co-workers, employing blood corpuscles labelled with radioactive phosphorus, the circulating blood volume has been determined on both normal and cardiac cases, with and without failure. A prerequisate for the determination of the circulating blood volume is that the dilution curves can be established and thereby the time when equilibrium appears.

In this work the results in each case are based on the mean values of a number of determinations. The mean value for the amount of the circulating blood corpuscles in normal cases was found to be 1850 c.c., 1998 g. or 33·4 g. per kilogram of body weight. The mean value for the compensated cases is in agreement with the normal values at 1795 c.c., 1939 g. and 31·8 g. per kilogram of body weight. The total blood volume in the normal cases is 73·5 c.c. per kilogram of body weight, and in the compensated cases 71·8 c.c. Two cases of heart failure—and particularly one of them—show a considerable increase in both the amount of blood corpuscles and the circulating blood volume. The other case has been followed with repeated determinations after all signs of failure had disappeared, a great decrease in the circulating blood volume of no less than 28 per cent taking place simultaneously with the appearance of the interesting phenomenon that the amount of red blood corpuscles also decreased by 18 per cent.

I proffer my grateful thanks to Professor G. von Hevesy for all his kind advice, and I am greatly indebted to Professor M. Siegbahn for supplies of radioactive phosphorus.

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SINUS BRADYCARDIA WITH CARDIAC ASYSTOLE

BY

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The case history of a patient suffering from attacks of cardiac asystole with syncope is described. On superficial examination the condition appeared to be one of Stokes-Adams disease; electrocardiographic tracings, however, showed that there was no delay or block in the conducting system of the heart, but a persistent sinus bradycardia (about 24 beats a minute) interrupted by complete asystole for periods of at least 22 seconds. No report of a similar case has been found. The effect of exercise and various drugs upon the heart rate is described and the underlying basis of the condition discussed.

The patient was a woman of fifty-two years. She had led an active life until the onset of the present symptoms. Apart from excessive menstrual loss for nine years after the birth of her child, she had no history of previous illness. The menopause took place a year before admission.

In February 1943 she first complained of occasional dizziness, particularly after stooping. At this time she was found to have a regular pulse rate of 24 beats a minute. These attacks became rather worse two months before she was first seen in December 1943. During this month while in her garden she had her first attack of loss of consciousness. She felt faint and fell to the ground before she was able to sit down. Three weeks later she lost consciousness for the second time just after a cardiogram had been taken. Following this she had two or three attacks weekly until her admission to hospital on 29/1/44.

At this time her pulse was forceful and regular at 24 beats to the minute. The heart sounds were normal, the blood pressure somewhat raised (195/105). Radiographic examination of the heart showed slight generalized enlargement. There was no evidence of arteriosclerosis.

Shortly after admission it was observed that her pulse was not always regular; additional beats were often present, sometimes occurring singly and sometimes in short runs of two or three. She felt faint frequently and was aware that her heart had ceased to beat or was beating irregularly. At times she lost consciousness: sometimes this happened without her knowledge, for example, on several occasions she realized that she had fainted only because the cup she had been holding had fallen from her hand; usually she was distressingly aware of imminent loss of consciousness. Her description of her sensations at these times was as follows: "In very mild attacks there is a feeling of dizziness causing me to stand still if I am walking and a feeling as if my body was leaving me." In more severe attacks " there is a feeling as if cotton wool was being rammed into my arms and as if my arms and legs were in clamps." During these attacks she felt very frightened.

Observation of these attacks, which were now occurring very frequently, confirmed the absence of pulse at the wrist during them, and on auscultation no heart sounds could be detected. The pause, which might last for from 5 to 22 seconds, was usually followed by several rapid, irregular beats before the normal rate of 24 beats a minute was resumed. Tracings during these attacks showed that there was complete standstill of the heart followed by an increased rate, partly due to extrasystoles. During the attack the patient's face became pale and then flushed as the pulse returned, so that even minor attacks could easily be recognized by observation from the end of the bed. In more prolonged periods of asystole consciousness was lost. In these, after the preliminary pallor, a look of fearful expectation would appear, followed by movement of the head and eyes to the right with clenching and sometimes grinding of the teeth and swallowing movements; at times she would take a sighing inspiration, the arms being flexed at the elbows and the hands raised in a series of jactitating contractions of the forearms and clutching movements of the hands. It was difficult to tell at what stage consciousness was lost, but on several occasions the patient continued to talk for at least seven

seconds after the pulse had become impalpable, before she stammered and ceased speaking. On three occasions standstill was observed to last for 22 seconds. After long pauses the cardiac contractions were especially vigorous and the head and shoulders were shaken by each pulsation which could be clearly seen in the carotid vessels. At the same time a deep flush spread over her face.

The patient thought that the attacks were worse after effort and particularly noticed that the use of a bed-pan or even talking in an animated way precipitated them. The frequency with which they occurred when she was being examined suggested the possibility of an emotional precipitating factor. Air raids, including the dropping of heavy bombs in the vicinity, had no effect except on one occasion. The patient was then aware that her heart had suddenly started to beat more rapidly, and the night nurse reported that the rate rose to 100 beats a minute and continued at this level for ten minutes but then returned to 20 beats a minute; this was the only occasion at rest under natural conditions when a rate greater than 30 beats a minute was recorded. Although she usually slept well at night, irregular beats and long pauses were noticed during sleep by the night nurse.

At times she would have a series of attacks, being scarcely out of one before the next took place, over a period of several hours. Sometimes she vomited during these bad periods. On 27/2/44 she was examined while having a series of attacks following a good night. The first occurred while the patient was on the bed-pan. When seen later the pulse was irregular, with periods of standstill up to 10 seconds followed by irregular and often coupled beats. The face was flushed and became pale repeatedly. The patient vomited several times. On 12/3/44 she was observed for forty-five minutes during which at least fifteen attacks occurred and on one occasion three periods of asystole lasting from 7 to 9 seconds took place in one minute, the first with loss of consciousness. During the last three months of her stay in hospital the attacks became much less frequent and usually followed exertion.

After her discharge from hospital in August 1944, she continued to have frequent faint turns and lost consciousness several times weekly. At this time she was staying with friends away from home and was worrying about her husband and daughter. For three weeks before she returned home at the end of October she had no loss of consciousness, although she was aware of short pauses, double beats, and runs of four or five irregular beats. On 29/10/44 when she was examined her pulse rate was in the region of 20 and periods of coupling were frequent when only alternate beats got through to the wrist. On this day the blood pressure when first taken was 230/110, but after an hour the systolic pressure had fallen to 180 mm. The Wassermann reaction was negative. The blood sugar during a series of attacks was within normal limits. The serum potassium was 21·6 mg. per 100 c.c.

Electrocardiographic tracings were taken on a number of occasions. These showed that the basic rate varied between 18 and 24. The complexes showed normal sinus rhythm. There was constantly a large T wave, particularly in the second lead. Periods of cardiac standstill were observed up to 9 seconds and were followed by a rise in rate to 50 or more for a few seconds. Exercise had a similar effect. Impulses frequently occurred in pairs from the S-A node, but on other occasions the coupling was shown to be due to auricular or ventricular extrasystoles. Isolated auricular and ventricular extrasystoles were often observed. There

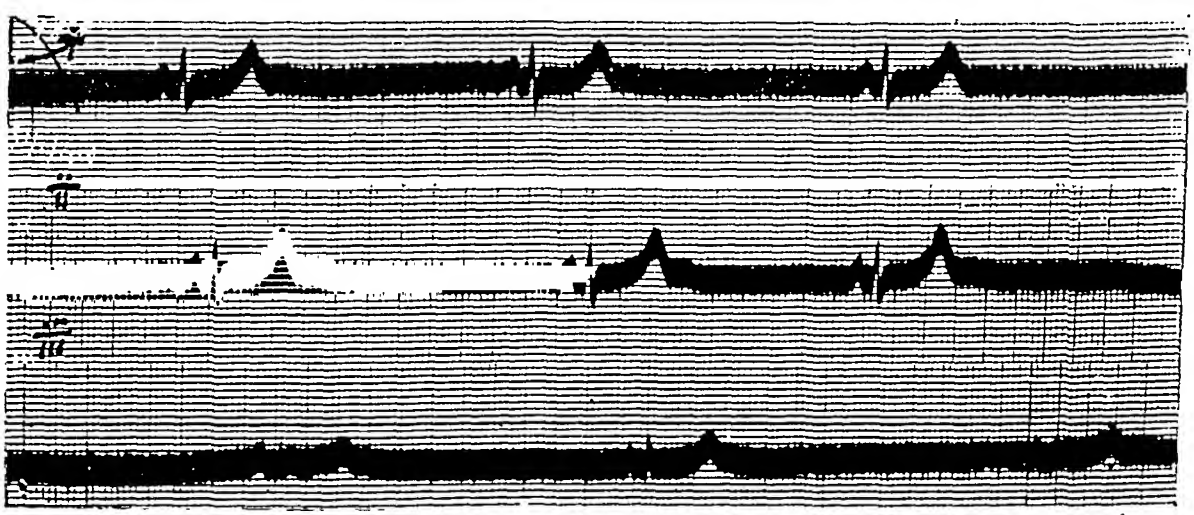

FIG. 1.—Electrocardiogram showing her usual basic rate of 24 a minute. All figures have been slightly reduced in size (43/50).

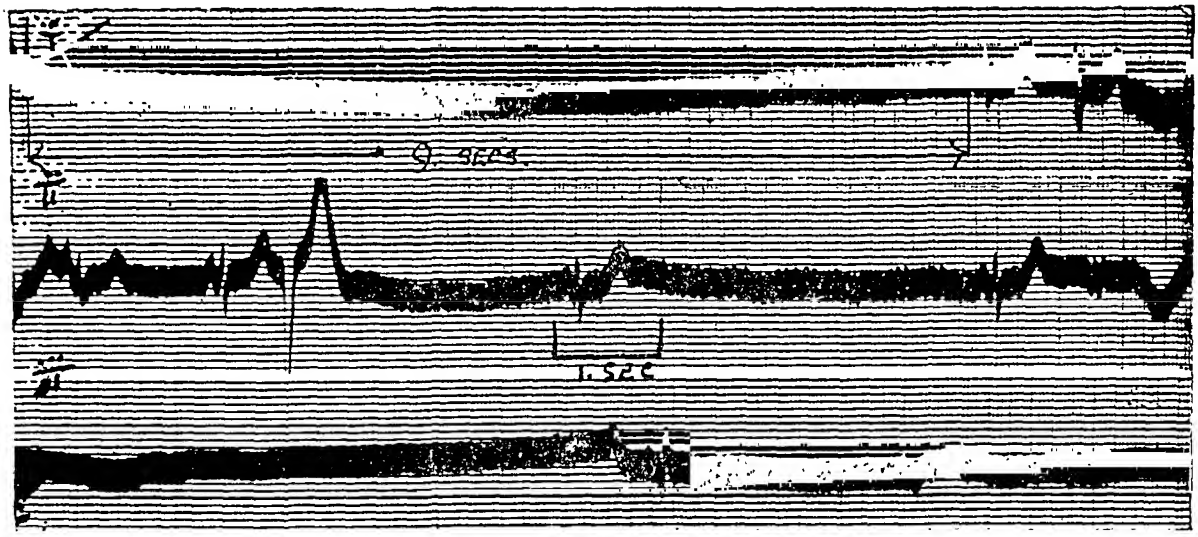

FIG. 2.—Asystole for 9 seconds in lead I. Lead II shows a ventricular extrasystole; lead III shows the end of a further period of asystole.

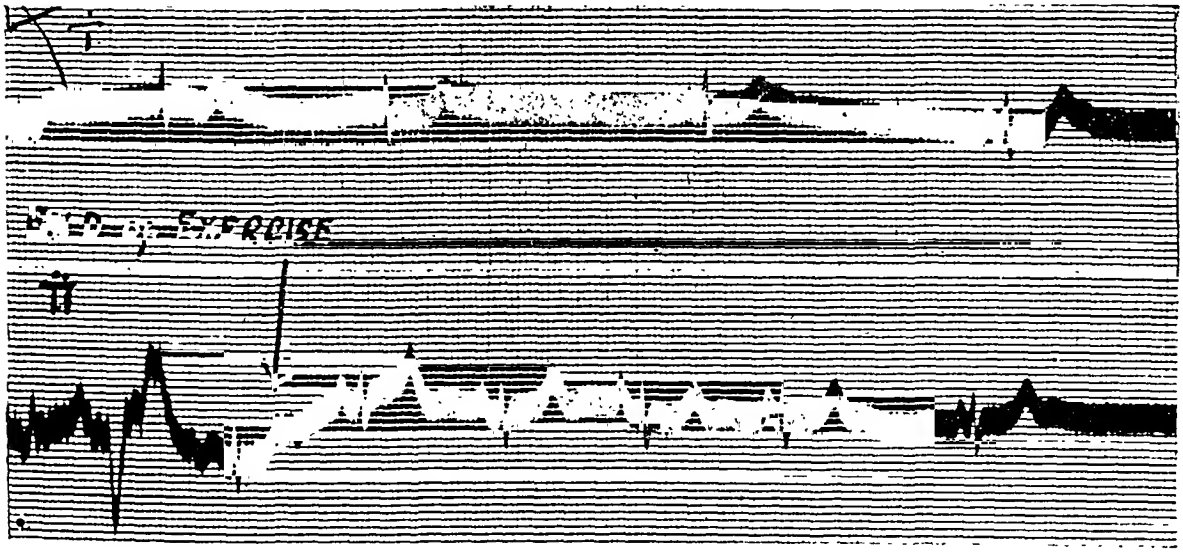

FIG. 3.—The increase of rate caused by exercise is shown in lead II.

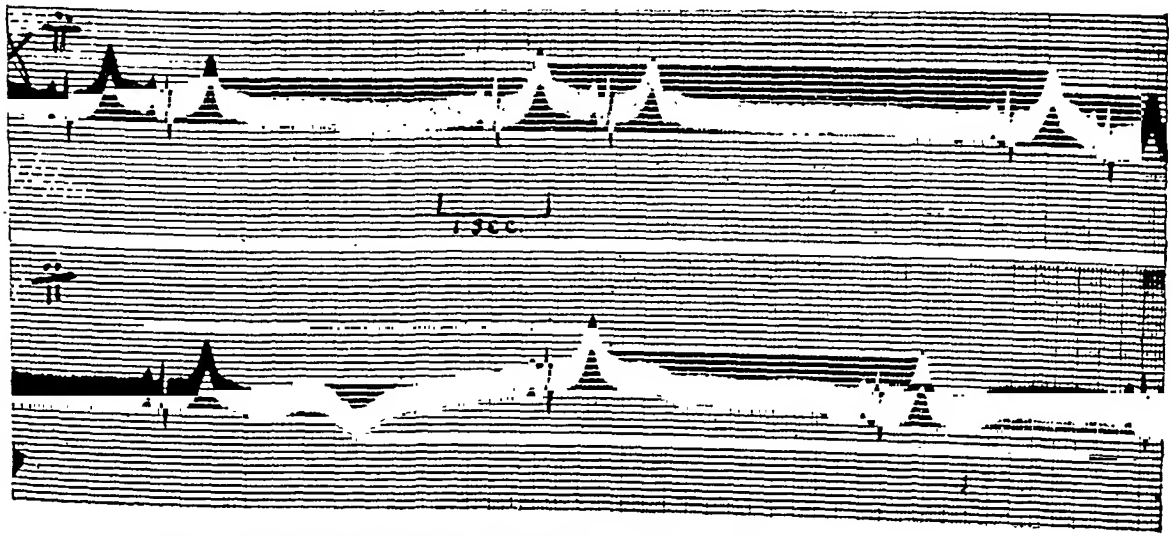

FIG. 4.—Coupled beats, the second being a premature beat arising from the sinus.

was no delay in conduction and no evidence of nodal escape or of ventricular rhythm during periods when the sinus failed.

On 22/6/44 a cardiographic tracing was recorded continuously for about half an hour, with a simultaneous electro-encephalogram. During this period every abnormality seen in previous cardiographic tracings was recorded. At times a regular rate between 18 and 24 beats each minute was observed. Premature beats giving rise to coupling at regular intervals sometimes occurred on from five to ten successive occasions, the extrasystole sometimes arising repeatedly from the ventricle, sometimes from the sinus or the auricle, and sometimes from varying sites after successive normal beats. On one occasion a period of asystole up to 12 seconds was followed by 15 ventricular extrasystoles in 11 seconds, on another 14 beats arising sometimes from the auricle and sometimes the ventricle were recorded in 10 seconds. Periods of asystole occurred frequently: on two occasions these lasted for 13 seconds, and once for 12 seconds. Asystole of 10–11 seconds occurred twice, 8–9 seconds three times, 7–8 seconds ten times, 6–7 seconds twelve times, 5–6 seconds thirteen times, and 4–5 seconds ten times. Such periods of asystole were followed by single normal beats, coupled beats, short runs of extrasystoles, or irregularly spaced beats with occasional ventricular extrasystoles.

The following example shows the extreme variations that could occur consecutively in 43 seconds—asystole for 7 seconds, a coupled beat, both impulses arising from the S-A node, an interval of 2·5 seconds followed by a normal beat and a ventricular extrasystole, an interval of 3 seconds, a normal beat followed by a premature auricular beat, asystole for 5 seconds, a normal beat followed by two ventricular extrasystoles in close succession, asystole for 5 seconds, a normal beat with a premature ventricular beat, asystole for 5 seconds, a coupled beat, both impulses arising from the S-A node, asystole for 4 seconds followed by another coupled beat from the S-A node, an interval of 3 seconds followed by a further coupled beat.

The *electro-encephalogram*, which was recorded simultaneously, was entirely normal except that after a period of asystole there were minimal change in rhythm due to cerebral anoxæmia. This investigation was carried out by Dr. J. D. N. Hill, for whose help I am grateful.

The following observations were made.

Effect of exercise. This was always followed by an increase of pulse rate for some seconds, but this was usually succeeded by periods of asystole. Very slight exertion caused extrasystoles or coupling and the pulse was always markedly irregular on these occasions. Rising from a lying to a sitting position ten times caused a very transient rise to 60 beats a minute. If the patient held her breath for 15 to 30 seconds similar irregular pulsation with gaps would occur,

Compression of carotid sinus. This had absolutely no effect on the pulse rate or blood pressure on a number of separate occasions when it was tried.

Effect of atropine. 1/50 of a grain of atropine was injected intravenously on 8/2/44. The pulse rate before the injection was regular at 20 a minute. After ten minutes the pulse rate had risen to 27, after fifteen to 31, after thirty to 31, after forty-five to 33. The mouth was then dry and the pupils widely dilated. The pulse rate remained at 33 to 34 until three hours after the injection and then gradually fell.

On 19/5/44, 1/25 of a grain of atropine was given intravenously. The pulse rate was regular at 20 before the injection. After five minutes it had risen to 34 beats at the apex. These were coupled and only 17 were counted at the wrist. This coupling continued for fifteen minutes. After twenty minutes the rate was regular at 32 at the wrist and apex. The vision was blurred and the mouth dry: after an hour the rate had risen to 34 and was regular. It continued at this height for several hours, but six hours after the injection had fallen to 25.

It was noticed that the blood pressure, which was 168/90 before the injection, rose to 212/90 after half an hour, to 208/90 after forty minutes, and had fallen to 190/90 after two and a half hours. As a result of this injection the patient suffered from transient mild symptoms of atropine poisoning and was hallucinated and disorientated.

Atropine in full doses, therefore, caused a slight increase in rate with a regular pulse. Medicinal doses (1/100 of a grain and regular heavy doses of belladonna) given when the patient was having frequent attacks of faintness had no obvious beneficial effect. The patient thought that periods of asystole were rather more frequent during this treatment.

Effect of injection of adrenalin. 5 minims of adrenalin was injected subcutaneously on

4/2/44. The pulse rate before the injection was 20. It rose to 27 after twenty minutes and was somewhat irregular at this time due to extrasystoles. On 29/10/44 the pulse was regular at 19 at the wrist, but with coupled beats audible at the apex for fifteen minutes before 5 minims of adrenalin were given. After five minutes the patient was trembling slightly but the pulse rate was unaltered and the beats were still coupled; after seven minutes 22 coupled beats were counted, after nine minutes 28; at eleven minutes the pulse became irregular with asystole of seven seconds followed by six or seven rapid beats. No further rise in rate occurred but the pulse became more irregular and periods of asystole of 5–7 seconds occurred once or twice each minute until half-an-hour after the injection, when the pauses ceased, coupled beats diminished, and a regular rhythm of 24 beats to the minute was observed twenty-seven minutes after the injection. Occasional coupled beats were felt after this but after 42 minutes the rate was regular at 28, and after 45 at 24 a minute.

Adrenalin, therefore, appeared to produce an effect resembling that of exercise, leading to a slight increase of rate, with periods of asystole.

Effect of ephredrine. Ephedrine, 1/2 grain given by mouth on 10/2/44, was apparently followed by some increase in the number of extrasystoles, although the pulse rate, which was 19 before administration, never rose to more than 22 during the next hour.

Effect of thyroxin. Thyroxin, 2 mg., was given intravenously on 7/5/44. The pulse rate beforehand was 18 and regular; blood pressure 152/80. After ten minutes the pulse rate was 16 and regular; after twenty minutes, 16 regular; after thirty minutes, 19 with three extrasystoles, systolic blood pressure 156; after forty minutes the pulse rate was 17 with 4 coupled beats. After an hour the pulse rate was 19 with 3 coupled beats; after 2 hours, 20 with 3 coupled beats; after 3 hours, 22 and regular. The rate continued between 23 and 24 for a number of hours. This dose of thyroxin had no obvious effect on the pulse rate.

The administration of acetylcholine or its derivatives was considered too dangerous owing to the possibility of increasing the periods of asystole. Their effect was not, therefore, observed.

The following drugs were given therapeutically. *Tinct. Belladonna*, up to 20 minims, four-hourly, had no obvious effect on the pulse rate but made the patient dry and uncomfortable; during the time she was on this preparation she had many faint turns. Injection of *atropine*, 1/100 of a grain, was likewise ineffective in preventing attacks of asystole. *Thyroid sicca*, 1/4 of a grain t.i.d., had no effect. *Barium chloride*, 1/2 a grain t.i.d., *Luminal*, 1/2 a grain t.i.d. by mouth, *Nicotinic acid*, 100 mg. daily, and *Benerva*, 50 mg. daily, given intravenously, had no obvious effect on the pulse rate. It was thought that the atropine preparations and the thyroid possibly led to an increase in the irregularity of the pulse and in the number of faint turns.

Discussion

Loss of consciousness with disappearance of the pulse at the wrist and absence of heart sounds is commonly due to one of three clinical conditions—simple fainting resulting from vaso-vagal disturbances, heart block (Stokes-Adams disease), or stimulation of the vagus nerve as the result of a sensitive carotid sinus reflex or more rarely by pressure from a tumour or aneurysm. The patient whose history has been recounted did not suffer from any of these conditions. Simple fainting is unlikely to occur at rest in bed, particularly during sleep, nor were the usual prodromal symptoms of salivation and perspiration ever recorded; there was no cardiographic evidence of heart block; the symptoms could not be reproduced by pressure over the carotid sinuses, nor were they prevented by atropine. Moreover, none of these conditions offers any explanation of the persistent bradycardia (varying between 15 and 30 beats a minute) known to have been present for seven months while the patient was in hospital and probably for at least two years.

Other rare causes of cardiac syncope have been described. In sino-auricular block, Type A (Cowan), the sinus stimulus may default so that auricles and ventricles miss one or more beats, and fainting may occur. The interval between successive beats is in this case always a multiple of the normal beat, i.e. it may be two, three, or four times the normal interval between auricular contractions. The pulse rate in S-A block is usually within normal limits,

but Cowan records the history of a man, aged 63, who suffered from syncopal attacks and had a basic heart rate of 30 due to a sinus bradycardia. This was thought to be the result of impaired blood supply of the S-A node following coronary infarction. Although this case is in many ways similar to ours, the absence of any regular mathematical relationship between the periods of asystole and the preceding pulse rate excludes sino-auricular block in the latter.

Laslett (1908–09) described the case of a woman, aged 40, suffering from fainting attacks due to arrest of the whole heart, as demonstrated by sphygmographic tracings of the jugular pulse. In this patient the basic rate was 60–70 beats a minute. Unconsciousness occurred if asystole lasted for more than 7 seconds. The irregularity of the intermissions in this case excludes S-A block. After atropine, 1/50 of a grain subcutaneously, the pulse rate rose to 100 and remained regular for a number of hours: exertion or excitement also temporarily prevented periods of asystole. Laslett concluded that increased vagus influence was responsible for the failure of the S-A node in this case.

Wedd also records the history of a boy, aged 16 years, complaining of fainting, in whom the heart rate varied between 32 and 86 with periods of standstill of from 3–7 seconds. The electrocardiogram showed, however, that the heart beat originated from the A-V node. This nodal rhythm persisted after atropine (1/33 of a grain), but periods of asystole were abolished and the pulse rate rose from 40 to 86. The periods of cardiac standstill appear to have been due to excessive vagal stimulation.

Trocmé (1922) describes two cases of sinus bradycardia with no increase of rate following atropine, and attributes the condition to hypo-excitability of the S-A node. Periods of asystole occurred, which he attributed to increased vagal tone.

This patient differs from most others with cardiac standstill due to rare disturbances of rhythm in the failure of atropine to abolish the periods of standstill or to raise the basic pulse rate to a normal level. This striking ineffectiveness of stimulation or paralysis of the vagus nerve to modify the heart's action suggests that the S-A node is less excitable than normal. The slight effect of exercise and other drugs such as adrenalin, thyroid, or barium chloride is further confirmation of this view. Trocmé's cases alone may have had a mechanism similar to ours.

The reason for the development of a condition of such reduced excitability remains obscure. There was some evidence that psychological factors might influence her condition, but it is unlikely that the condition could be explained on this basis. In view of the patient's age, diminution of the blood supply to the region of the pacemaker as a result of atheroma seems to be the most probable cause. On the other hand the failure of the A-V node or of the ventricle to initiate their own rhythm during periods of prolonged asystole may indicate a general condition of hypo-excitability.

Summary

A case of persistent sinus bradycardia with syncopal attacks due to cardiac standstill is described.

Evidence is given for believing that this is not vagal in origin but due to hypo-excitability of the pacemaker.

I should like to thank Dr. Terence East and Dr. Parkinson for their helpful advice.

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LIGATURE OF PATENT DUCTUS ARTERIOSUS

BY

GEOFFREY BOURNE

Received February 6, 1945

The effect of ligation on infection of the patent ductus has been admirably summarized from the surgical point of view by my colleague, Mr. O. S. Tubbs (1944). His paper, which gives a valuable account of the anatomy, physiology, and pathology of the ductus arteriosus, is based upon nine infected cases, eight of which were treated by us in collaboration. The purpose of the present paper is to discuss certain medical aspects of these cases and of two additional non-infected cases, also submitted to operation. Details of the individual infected cases are already published in Mr. Tubb's paper, and are referred to here by the same numbers as those used in that paper and in that of Bourne, Keele, and Tubbs (1941).

Infected Cases

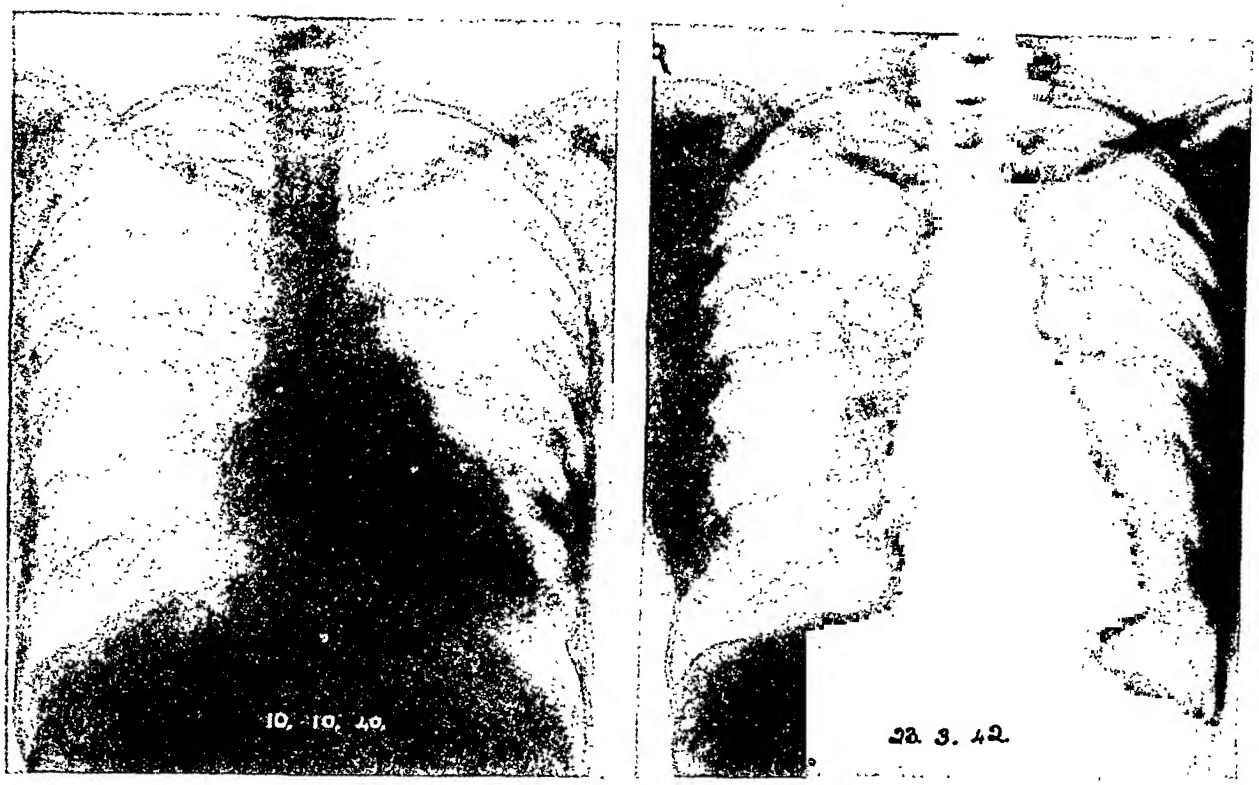
Dr. Keele's case, Case 1 of our series (Bourne, Keele, and Tubbs, 1941) was the first infected case recorded that was cured by ligature of the ductus arteriosus. The date of the operation was December 5, 1939. Of the first five patients of our series, four are alive and well, from five to three years after the operation, with no recurrence of symptoms, of infection, or of cardiac disability. The permanent value of the operation is thus proved.

The infecting organism in Case 1 was *H. para-influenzæ*, and in seven other cases it was *Streptococcus viridans*. In one case (Case 8) the infection was apparently mixed, *Staphylococcus aureus* and *Streptococcus viridans*.

Although the number of cases is not large, certain observations, even if made in a single case, are so significant as to be worth recording, and may even form the basis of legitimate deductions. The extent to which these deductions are true, and the proportion of cases in which the observed phenomenon occurs must, of course, be determined by the study of a much larger number of cases.

Heart Size. The late result of ligature on the heart size is well shown in the X-ray photographs taken in Case 2 (Fig. 1). The first picture, dated October 10, 1940, shows an enlarged heart, the transverse diameter of the heart measuring 14·25 cm. and that of the thorax 24·75 cm.; it also shows typical enlargement of the pulmonary conus. The second picture, dated March 23, 1942, shows the transverse diameter of the heart to be 12·25 cm. and that of the thorax 24·75 cm.; the heart contour has become normal and the conus is no longer enlarged. This shows that ligature of the patent ductus can cause a reduction in heart size similar to that observed by Drury (personal communication) in animals in which an experimental arterio-venous aneurysm had been produced, and by Hitzig (1935) after ligature of arterio-venous aneurysm in man.

Thrill and Murmur. The classical thrill and murmur are generally ascribed to the rapid flow of blood from the aorta to the pulmonary artery. This presumably occurs when the aortic pressure is higher, i.e. during systole and early diastole. Compression of the patent ductus during operation obliterates the thrill in nearly every case, and this largely confirms the above theory of its causation. The following observations suggest that this explanation is not complete. Firstly, in Case 2, application of one ligature only reduced, but did not abolish, the thrill; this disappeared only after a second ligature had obliterated more of the lumen of the ductus. Secondly, in the same case, the diastolic murmur at first disappeared,



A B

FIG. 1.—Reduction in size of the heart after ligature of the patent ductus arteriosus (m.t.d. reduced from 14·25 to 12·25 cm.). (A) 10/10/40. (B) 23/3/42.

but returned, much less in volume, seventeen months after ligature, although the transverse diameter of the heart had diminished by 2 cm., and although the blood pressure remained perfectly normal (Fig. 1). Thirdly, in Case 4, the diastolic murmur disappeared for two weeks and then fully returned; yet, at the post-mortem examination seven weeks after operation, the pulmonary end of the ductus was found to be so blocked by a massive clot that water injected into the aorta failed to pass. There was, however, an aneurysm of the ductus, patent to the aorta and 3 cm. in diameter. Finally, Shirley Smith's observations (1929) on cases of patent ductus in infants, in which the typical thrill and murmur were absent during life, may be relevant to this problem.

The general deduction would appear to be that, although the thrill and murmur are largely caused in the usually accepted fashion, this is not the whole explanation. Patency of the ductus may occur without these signs, and these signs may be present without patency, although such conditions are exceptional.

The Blood Pressure. Immediately after ligature, a great rise in the diastolic and a lesser rise in the systolic blood pressure was observed. The figures for the changes in diastolic pressure (in mm. of mercury) in the first six cases were as follows: Case 1, from 60 to 120; Case 2, from 40 to 122; Case 3, from 58 to 108; Case 4, from 56 to 90; Case 5, from 64 to 98; Case 6, from 52 to 102; the average rise being from 55 to 107. This diastolic increase above normal may last for some weeks (Bourne, 1941), and therefore it is probably due to factors other than the increased blood volume. The cardiac hypertrophy, or an increased peripheral vascular tone, or both, may be causative factors. An associated state of temporary renal failure has been noted (Bourne, 1941). The sudden blood pressure change did not cause symptoms in any of the patients.

The Effect of Ligature upon Infection of the Ductus. Ligature is the only proved curative measure available. Without it the condition is usually fatal. Only two cases of recovery without treatment by ligature are on record (Chester, 1937; and Touroff and Tuckman, 1942). Of the present series of nine infected cases treated by ligature six are alive and well, from five to nearly two years after the operation. The results obtained in Case 5 demonstrate that ligature of the ductus can, of itself, bring about the disappearance of the infection,

for in this case all other forms of treatment were withheld. Seven days after ligature, the patient became completely afebrile, and the blood culture, which had previously been positive, showing the presence of *Streptococcus viridans*, became negative and remained so.

The Effect of Chemotherapy. The results obtained by the use of drugs were disappointing. In one case only (Case 2), sulphapyridine sterilized the blood and removed the fever for the twelve day period preceding operation. In Case 1, where infection was due to *H. parainfluenzæ*, sulphapyridine was ineffective. In six cases of infection by *Streptococcus viridans*, sulphanilamide, sulphapyridine, sulphathiazole, sulphadiazine, and sulphamezathine given in full doses produced no effect. One or more of these drugs was tried in each case. In one case (Case 8) infected by *Staphylococcus aureus* sulphathiazole failed.

This suggests that no advantage is obtained by instituting chemotherapy before operation if the condition of the patient is reasonably good. Chemotherapy, however, should be used to modify the severity of the toxæmia, before operation, in patients who are critically ill. It is also of value after operation, when infection persists. Infection may persist at the pulmonary end of the ductus, or in metastic and embolic infection in the lung. Chemotherapy, clearly, should be tried also if the post-operative fever is due to infection of the mitral or aortic cusps, although here the effect is problematical.

Prognosis in Cases Treated by Ligature. The ultimate prognosis is good, considering the seriousness of the condition. Experience in the surgeon and skill in the anæsthetist are, of course, vitally important. From the small series of cases here recorded certain ideas concerning prognosis suggest themselves.

The degree of illness is a clinical matter, and is hard to evaluate scientifically. But in Case 3 the patient was desperately ill, and by ordinary criteria was an unsuitable subject for a surgical operation. None the less this was decided upon, and the patient made a good recovery. The comparatively small risk of operation in these ill and toxic patients is also stressed by the fact that no death occurred on the table. One patient died 45 minutes after the operation. The other two fatal cases, both of whom had severe secondary pulmonary sepsis from infected pulmonary emboli, survived the operation by seven weeks and by four months respectively.

It may be significant that Cases 4 and 7 had marked cardiac enlargement ; both died. In Case 9, the other fatal case, the heart was only slightly enlarged, and infection of the aortic valve was present.

Pulmonary embolism and infarction in this condition is of two varieties, that occurring from the growing vegetations, and that resulting from the fragmentation of clots or vegetations during the healing process. The former occurs before, and the latter after operation. Pre-operative embolism, with pleurisy, either with radiological change or visible or palpable at operation, was present in seven of the nine infected cases. Its presence, therefore, does not seem to influence the prognosis. Post-operative embolism in convalescence is common and is equally free from serious danger.

In two of the three fatal cases, an aneurysm of the pulmonary artery (3 cm. in diameter in Case 4, and 1·5 cm. in diameter in Case 9) together with multiple pulmonary infarcts was present. In two fatal cases, left-sided endocarditis was found at autopsy, aortic endocarditis in Case 7, and mitral and aortic endocarditis in Case 9.

The increased virulence of infective endocarditis in children also seems to influence the outlook in the case of this lesion. The two youngest patients, aged 10 and 15 years, died.

These factors must all be remembered in estimating the possible result of operative treatment.

Ligature of Non-infected Cases

A large number of uninfected cases have been treated by ligature and have been reported by several authors. Indications for this operation would seem to be mainly:

(1) the anticipation of subsequent infection,
(2) the threat of heart failure, or
(3) in children, the failure to grow normally.

It is highly probable that the risk of subsequent infection can be prevented by this operation.

The figures given by Maud Abbott (1936), showing that infection developed in 29 per cent of 73 cases over the age of two years, suggest that the chance of subsequent infection is great. It is also true that the operative risk is less in the uninfected cases, the uninfected ductus being less fragile. On the other hand, the procedure is not without danger. Future developments in chemotherapy, or treatment by penicillin, may strengthen the conservative attitude of watching such cases and reserving surgical treatment until the actual onset of infection. This is the writer's policy in this matter at present. [Since the date of writing one case, treated with penicillin, before operation, became afebrile in 36 hours.]

The two following cases have not been described previously. In one, a woman of 24 years of age, heart failure was present. The history was that she had always been short of breath on exertion, and that this had been increasing slowly up to the point when she would have to stop after climbing about five steps. Orthopnœa had also been present. Three months previous to operation, œdema of the feet and legs had appeared and had been increasing. The lesion was considerable, for the heart was large. The heart diameter was 15 cm. and that of the chest 30·5 cm.; the blood pressure was 140/54. Since operation she has been better than ever before in her life. During this period of one year and seven months she has done war work for nine hours daily in a factory, often including Sundays. She was able to remain at work for six months of pregnancy without symptoms. She had previously had two children, but her life had been that of a partial invalid. Thus, ligature of the ductus would seem to be indicated for the relief of early congestive failure.

The other case was that of a child of nine years. She was symptomless, but was undeveloped for her age compared with two older brothers, and the heart was a little enlarged. Her father, a doctor, had a lively realization of the risk of infection. In this combination of circumstances operation was decided upon. Unfortunately, the ductus was of the stoma or " window " type, having no length at all. This rendered ligature impossible. The danger of the ductus being of the stoma or " window " type must be taken into account in assessing the operative outlook, either clinically or in discussion with patients or relatives both in infected and in non-infected cases.

Conclusions

In infected cases of patent ductus arteriosus, successful ligature of the ductus brings about a lasting cure.

In non-infected cases (of which I have less experience) it may be most successful even at the stage when heart failure is developing.

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LIGATION OF THE PATENT DUCTUS ARTERIOSUS

BY

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This operation is now being performed to cure patients who have become infected, but also it may be done to remedy a congenital defect, which very considerably reduces the prospects of longevity, and is as well the source of several serious disadvantages.

This is an account of the experience provided by thirteen cases, considered from the medical point of view. All the operations were done by Mr. John B. Hunter, F.R.C.S., and Dr. Nosworthy gave the anæsthetic.

Diagnosis and Prognosis

Diagnosis presented no difficulty: the typical murmur, best heard in the second left intercostal space, starting just after the first sound and persisting into diastole (with the exception of one case where it is doubtful whether it would be heard beyond the second sound), was present in all. This applies to two other cases seen during the same period, who declined operation. Its hollow whizzing character resembles nothing else to my ear. Is not " machinery murmur " a bad expression? I cannot think of any machine causing such a sound. In most a thrill was palpable as well. Sometimes there was a systolic pulsation, and as a rule the pulmonary second sound was loud and the closure palpable. The pulmonary artery was never large enough to cause dullness. The possible presence of another congenital defect, in particular pulmonary stenosis, was always considered but was never suspected. A normal cardiogram, and the absence of its peculiar murmur lower down should exclude pulmonary stenosis. Obviously, if this were present, ligation of the ductus would be undesirable.

All the cardiograms were within normal limits.

Enlargement of the pulmonary artery in the skiagram may be quite conspicuous, but in this series of thirteen cases it is clear from the outlines shown in the figure that nothing very striking may be noted. In Case 4 the pulmonary artery was largest, and that has a flat curve.

Enlargement of the heart was present only in Case 3 and perhaps in Case 2. But in this series the disease was in its early stage, and failure had in no case come on. The blood pressure readings showed no constant abnormality, but an average figure of 120/70 indicated a slightly increased pulse pressure. In some the diastolic pressure tended to be low.

Physical examination before operation gave no reliable information as to the size and shape of the ductus.

Probably in most cases, until well into adult life, a patent ductus arteriosus may interfere but little with activities. But such a lesion as this is almost certain to be recognized early in life, and in many instances restrictions that are probably unnecessary are imposed. The result is that the patient is well aware that there is something wrong with him, and may become unduly heart-conscious and even neurotic. He will certainly miss a great deal of the best that youth can give.

Later on more serious considerations arise. Employment in many walks of life will be hard to obtain. The Services, civil and military, will be closed to him; banks and many firms will not employ him because he is ineligible for staff schemes and pension funds. Life assurance will be denied him. Strenuous occupations will be unwise; a woman may be

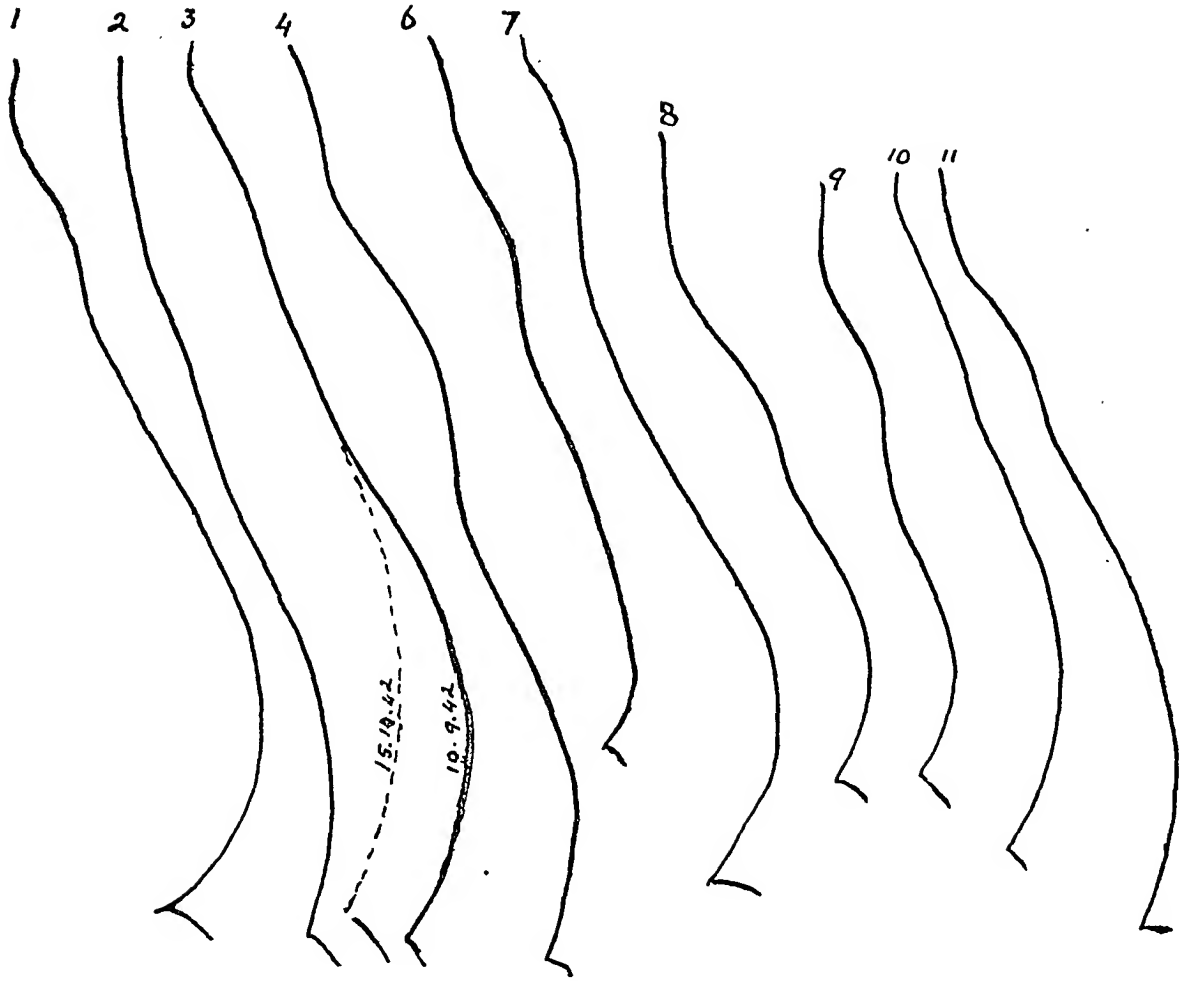

FIG. 1.—Outlines of the left border of the hearts, before and after operation, in patent ductus arteriosus. The numbers correspond with those of the cases.

advised against marriage and certainly against pregnancy, although she would probably accomplish this well enough.

Ultimate Prognosis. The danger of infection in these patients is considerable. Although for the most part they seem to reach the twenties without disability, they are rarely seen in middle age. I cannot recollect having seen one over the age of forty. Heart failure no doubt accounts for the early death of many.

CHOICE OF OPERATION AND RESULTS

The experience of this small series makes one conclude that ligation of the patent ductus arteriosus by a surgeon skilled in thoracic surgery, aided by an anæsthetist who has practised the technique that this work requires, is not a dangerous procedure. The small pneumothorax or hydrothorax, which sometimes appeared, very soon cleared up with the help of breathing exercises. In no case was there any anxiety about the patient after the operation. Breathing exercises were always given on or soon after the third day. Unquestionably the children were least affected, and tolerated the operation very well.

Age for Operation. Any time in childhood, as soon after the sixth year as possible for preference, seems to be the best. I believe that my colleague, Mr. Hunter, who is describing these cases elsewhere from the surgical point of view, is of opinion that for technical reasons the operation is easier in children. Certainly it would be an advantage to cure this defect as soon as possible in order that its undesirable effects on mental and physical development may be eliminated while the child is growing. It is obviously a good thing to have as normal a childhood as possible.

In all these patients the signs of the patent ductus disappeared (with one exception, for reasons given). It was the practice of Mr. Hunter, before ligation, to press on the ductus with his finger and note the disappearance of the thrill. This was always there, even if it could not be felt on the chest wall.

The contour of the heart showed very little change in subsequent skiagrams, except in Cases 2 and 3 where the ventricles decreased a little in size, and in Case 9 where the curve of the pulmonary artery became a little flatter. In these cases, where before ligation no gross degree of abnormality was apparent, little change is to be expected.

Effects of Operation. The young adult is certainly relieved to feel that his disability is cured, and that his heart is normal, although, of course, he does not know his medical prognosis. To be free from the various disadvantages detailed above is obviously a benefit.

Whether there remains any risk of infection on the dimple that I suppose persists at either end of the ligated ductus, one cannot yet say. One must not press the analogy too far, but infection on the pits and excrescences of an atheromatous aorta is very uncommon, and primary infection on the right side of the heart is very rare. The favourite site for infection is where blood passes through a small hole. For instance, organisms attack the patent septum of Maladie de Roger often enough, but not that found in Fallot's tetralogy.

One may hope that the risk of infection after ligation is negligible.

In some children a patent ductus arteriosus seems to retard mental and physical development, and it must be desirable to obviate this.

To leave operation until heart failure has set in, when the patient is probably well into adult life and the procedure less easy and more risky, is surely a mistake. To wait until infection has occurred is dangerous, for although brilliant cures have been effected, they cannot be relied on.

Summary

Ligation of the patent ductus arteriosus has been performed in thirteen cases. No anxiety arose in any case following operation. One patient, infected before operation, died later. One other patient died of septicæmia which started after nine days normal convalescence. It may possibly have arisen as a result of the operation, but there were no direct evidence of this.

The conclusion is that ligation is a good method of treatment in any patient with patent ductus arteriosus; the sooner after the sixth year, the better.

Appendix of Case Notes

Case 1. Male, aged 16. Drayman's apprentice. He was of rather poor physique and somewhat slow mentality. He had lived an ordinary life without symptoms, but had been rejected by the Air Training Corps Board.

A typical murmur was heard above the pulmonary area just after the first sound, extending faintly into diastole. There was no thrill. The pulmonary second sound was loud. The pulmonary artery was enlarged and there was a slight pulsation in the hilar vessels. The heart was not enlarged. B.P. 144/40–135/80. Electrocardiogram (EC.) normal. There was functional albuminuria. Blood urea, 24 mg. per 100 c.c. Specific gravity test and urea clearance were normal.

At operation the ductus was estimated as being about 10 mm. × 6 mm. The thrill over it disappeared at once on pressure, and permanently on ligation.

After operation the pulse rose to 140, but was down to 80 on the fourth day. The blood urea rose to 41 mg. per 100 c.c. on the fourth day, but fell to 22 mg. per 100 c.c. on the seventh day. A small local pneumothorax appeared at the left apex and a small hydrothorax at the left base. These cleared up in the following three weeks, breathing exercises being given as soon as possible.

He left hospital eight weeks after operation, having gained 4 lb. The ductus murmur had disappeared, though a faint systolic was heard for a time. He seemed to be much more lively towards the end of his stay. At no time was there any anxiety about him and he tolerated the operation well. When seen again three years and nine months later, he was a flight-sergeant in the R.A.F., shortly to undertake operational duties. The skiagram showed no change in the cardiac outline. B.P.120/80.

Case 2. Female, aged 18. Clerk. She had never had any symptoms, but since the discovery of the lesion at the age of five, had been kept from strenuous activities She was well-built and of normal mentality. She had been referred by a medical board under the Military Training Act.

A typical murmur, occurring late in systole and persisting through diastole, was audible in the second and third left spaces. A thrill was felt. The pulmonary second sound was loud. The heart was not enlarged (12·25 cm. in diameter) but the pulmonary artery was a little full. B.P. 120/70.

At operation the ductus seemed to be about 10 mm. × 6 mm. The thrill disappeared at once on pressure and ligation. Afterwards the pulse did not rise above 110. A small hydrothorax appeared at the left base. Blood urea on third day, 26 mg. per 100 c.c. She was up on the twelfth day and left after five weeks, the fluid having quickly disappeared. Only a faint systolic murmur could be heard in the pulmonary area. The case gave no anxiety at all.

When seen two and a half years later she was very well, and particularly pleased to feel she was normal. The contour of the pulmonary artery was unchanged; the transverse diameter was 11·75 cm. B.P. 110/80.

Case 3. Female, aged 25. Lift attendant. The lesion had been found in childhood and she had lived a somewhat restricted life, with liability to undue dyspnœa. She had been referred under the Military Training Act. She was of normal build and mentality.

The usual typical thrill and murmur were present, with a loud and palpable pulmonary closure. The heart was somewhat enlarged, transverse diameter 13·5 cm., and the shadow of the pulmonary artery was slightly increased. B.P. 120/50, 120/80. EC. normal. Kidney function normal.

The operation (24/9/42) was followed by no complications, and there was but little discomfort. The pulse did not exceed 110, and she left in a month. The murmur had completely disappeared.

Two months later she felt very well, and was pleased to be normal. The transverse diameter of the heart was 12·5 cm. and the shadow of the pulmonary artery was a little smaller. Probably as a result of enemy action, it has been impossible to trace her, for her home has been destroyed.

Case 4. Female, aged 31. Lorry driver. She had always been breathless on anything more than slight exertion, and had never played any games. Lately the dyspnœa and palpitation had been worse, but this was probably mainly due to hypochromic anæmia (66 per cent Hb.).

There was a characteristic low-pitched persistent murmur, with thrill, and some systolic pulsation above the pulmonary area, with a very loud second sound. The pulmonary artery was rather large. The transverse diameter was 12·25 cm. B.P. 120/85. Kidney function normal. EC. normal.

The thrill ceased when the ductus was tied. After operation the pulse rose to 120 on one occasion. A small effusion formed in the mid-zone but soon cleared, and she left after a month. A slight systolic murmur persisted.

When seen twenty-six months later she was very well, and free from dyspnœa. The transverse diameter and the curve of the pulmonary artery were unchanged. B.P.120/90. No murmur was heard.

Case 5. Female, aged 10. (*Dr. C. Shaw.*) A thin, puny child, not robust, weighing 45 lb. Mentally very alert and intelligent. She had had no symptoms, except liability to asthma.

There were the typical murmur and thrill of a patent ductus arteriosus, with loud palpable pulmonary closure. The heart appeared to be slightly enlarged. B.P. 110/56–120/70. EC. normal.

Before operation the heart rate was very unstable, varying between 130 and 80. After operation there was an increase to 160 for a short time; but the rate soon settled and was much steadier than before. The ductus was funnel-shaped, base towards pulmonary artery, and about 7–9 mm. wide and 11 mm. long.

The signs of patent ductus disappeared after ligation, only a faint systolic whiff being audible. A small pneumothorax at the left apex and small effusion at the left base cleared up in a fortnight with the help of breathing exercises, and she left hospital three weeks after operation, having gained nine pounds in weight. The case caused no anxiety for the operation was well tolerated.

Two and a half years later her mother reports that she is very well, growing fast and learning tap dancing. She now weighs 82 lb.

Case 6. Female, aged 9. (*Dr. W. Sheldon.*) Thin asthenic child, weighing 54 lb., of normal mentality, eighth in family. There had been no symptoms, and she had played the usual games.

There were the typical murmur and thrill of patent ductus, with very loud and palpable pulmonary closure. The pulmonary artery was enlarged but not the ventricles. EC. normal. B.P. 120/60.

For a few hours after operation the heart rate was 140, but it soon settled. There were no complications and she left hospital on the fifteenth day. The murmur had completely disappeared.

When seen two years later she was well. The parents were particularly pleased with her progress at school, where she had recently won a scholarship. Her intelligence quotient rose 21 points five

months after operation. She had become more lively and active. She now weighed 69 lb. B.P. 140/60. Radioscopy showed that the pulmonary artery now had a normal contour.

Case 7. Female, aged 21. (*Dr. J. Maxwell.*) Well-developed young woman of rather neurotic mentality. Her activities had always been restricted, and latterly she had been too breathless to do much.

There were the harsh continuous murmur and thrill of patent ductus above pulmonary valves; there was no cardiac enlargement, and the contour of the pulmonary artery was normal. B.P. 110/85. EC. normal.

At operation the ductus was found to be short and wide. The next day the murmur had gone, breathing was easy, the pulse did not exceed 100. She left hospital twenty-four days after operation; there were no pulmonary complications.

Six months later she could do more; skiagram of heart unchanged in outline. Nineteen months after operation she had not started work, but that seemed to be due to her cardiac neurosis.

Case 8. Male, aged 6. (*Dr. W. Sheldon.*) An active child in good condition, weighing 55 lb.

Above the pulmonary area there was a characteristic continuous murmur of a patent ductus, with slight systolic pulsation and a loud second sound. There was a slight suggestion of a pulmonary reflux. No thrill was palpable. The heart was not enlarged, but the pulmonary artery showed some enlargement. EC. normal. B.P. 110/65.

After operation the heart rate rose to 130 for a day or so. He was very little affected. Breathing exercises were given and he was up on the seventh day. There were no pulmonary complications. He left after eight weeks in hospital, having gained 4 lb. The murmur disappeared at once, but an exocardial click persisted.

When seen eighteen months later the shadow of the pulmonary artery was unchanged, but the closure was no longer palpable. He was very well and had grown a good deal.

Case 9. Male, aged 6. (*Dr. W. Sheldon.*) A small, dull child, weighing 35 lb. There had been dyspnœa on exertion.

Above the pulmonary area there was a continuous murmur of patent ductus. The heart was not enlarged; the curve of the pulmonary artery was slightly increased.

The operation was done under avertin. Afterwards the pulse rose to 130 for two days. There was slight surgical emphysema and some transient collapse at the left base. This soon cleared up with breathing exercises, and he left hospital on the tenth day.

Nine months later his parents wrote saying that he weighed 40 lb., and that his breathlessness had gone; and that he seemed much more grown up since the operation and was very quick at school.

Case 10. Male, aged 7. (*Mr. J. Hunter.*) A small boy, dull and slow and backward mentally, weighing 60 lb. A typical murmur was heard, but no thrill was felt; the pulmonary second sound was not particularly loud: there was no pulsation. Heart was not enlarged. B.P. 115/85. EC. normal.

The operation was followed by no complications and he left hospital on the seventeenth day. The murmur had entirely disappeared.

This case is too recent for any subsequent progress to be of interest yet.

Case 11. Female, aged 12. (*Dr. W. Sheldon.*) Some complaint of breathlessness and palpitation: found she had to stop doing things before the others in the physical training class. A well-built girl, weighing 7st. 4 lb.

The murmur was hardly audible in diastole. There was no thrill. The heart was not enlarged (transverse diameter 11 cm.). B.P. 135/70. EC. normal. Pulmonary artery rather large in skiagram.

At operation the ductus was found to be large. The pulse reached 120 for one day, but soon subsided. A small hydropneumothorax followed, with some infection needing sulphapyridine, but it was quickly controlled. She left hospital on the twenty-fifth day. A year later she was reported to be very well, and had gained 10 lb.

Case 12. Female, aged 5. (*Dr. W. Sheldon.*) A small, thin child, weighing 30 lb. Her mentality was normal for the age.

The characteristic thrill and murmur were present, just above the pulmonary area. B.P. 100/55, 100/70. The heart was not enlarged, and the pulmonary contour normal. EC. normal.

After ligation the thrill at once disappeared, and later the murmur was found to have gone. Breathing was easy though the pulse reached 120. No complications occurred; but on the tenth day a high fever started, which was found to be due to staphylococcal septicæmia. Of this she subsequently died, in spite of sulphonamides and penicillin. No post-mortem examination was allowed; the

source of the infection remained obscure: whether as regards the operation it was "post" or "propter" cannot be said, but such infections not uncommonly arise without apparent cause, and for ten days nothing went amiss.

Case 13. Female, aged 26. This patient came in with infection of a patent ductus arteriosus. This had started about the time of a tooth-extraction two months before. The infection was due to *Streptococcus viridans*. The usual murmur and thrill were present. B.P. 155/65. The heart was not enlarged.

The ductus was ligated without complications. For a few days the murmur disappeared but later it returned. Infarcts appeared in the lungs, and the signs of an infection of the aortic valves were detected. In spite of courses of sulphonamides she ultimately died. At autopsy it became clear what had happened. The ductus was not effectively closed because it was too full of vegetations. The pulmonary artery and valves were extensively affected, and there were vegetations on the aortic valves. The murmurs that again became audible arose from the imperfectly occluded ductus and later from the diseased pulmonary artery and valves and from the aortic valves.

The fatal ending in this case is an argument in favour of prophylactic ligation.

MORPHINE HYPERSENSITIVITY IN KYPHOSCOLIOSIS

BY

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From St. Thomas's Hospital

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It has been recognized since the time of Hippocrates that patients suffering from " hump back " die young. The first descriptions of early death in persons suffering from severe kyphoscoliosis did not incriminate the cardiovascular system, and it was not until the end of the last century that continental observers described heart failure as being the most frequent cause. In 1930, Coombs made one of the first contributions to the English literature in a paper entitled, " *Fatal cardiac failure in persons with angular deformity of the chest.*" More recently, in America, Chapman, Dill, and Graybiel (1939) have investigated twelve such cases, and in a review of others reported, showed that the average age at death was only thirty years. The purpose of this communication is to describe three patients whose deaths while in cardiac failure are believed to have been precipitated by the administration of morphia.

Case Notes

Case 1. Male, aged 36; a hunchback as long as he could remember. He attended a school for physical defectives, but nevertheless played cricket and football. After leaving school, he led a comparatively normal life as a costermonger until the age of 30, when he was admitted to hospital complaining of increasing dyspnœa on exertion, and of hæmoptysis.

On examination, a gross mid-dorsal kyphoscoliosis to the right. Pulse 86, regular. Slightly cyanosed. Neck veins engorged to within one inch of the angle of the jaw. Fine crepitations at both bases. Moderate œdema of both ankles. Liver palpable, but not tender. Heart enlarged to the right and left. Heart sounds normal. No murmurs. Blood pressure, 180/130. Retinæ normal.

He was treated with Guy's pill and mercurial diuretics, and discharged three weeks later, having recovered from his failure. He felt well, and was working for two-and-a-half years before he was again admitted in failure. He was then orthopnœic, with a regular pulse rate of 90, and a blood pressure of 170/140. An X-ray photograph of his chest showed marked enlargement of both ventricles, and pulmonary congestion. An electrocardiogram was within normal limits. On the evening of his admission, he was given oxygen by B.L.B. mask, and morphia, 1/4 of a grain, for the first time, The respirations became increasingly shallow, and death occurred in one hour.

Post-mortem examination. Heart weight, 606 g. Both ventricular walls markedly thickened. Moderate atheroma of the pulmonary arteries. Coronary arteries and aorta normal. Lungs: left more emphysematous than right; both congested.

Case 2. Male, aged 36. He complained of increasing dyspnœa for two months. His back had begun to be " humped " at 24 years of age. This had gradually increased to reach its present severity six years ago.

On examination, orthopnœic, with cyanosis. Ventricular rate 88, auricular fibrillation. Neck veins engorged; marked œdema of legs and sacrum; crepitations at both bases. Heart enlarged one inch to right of sternum. Pulmonary second abnormally loud. No murmurs. Blood pressure 110/70. Retinæ normal. A very marked mid-dorsal kyphoscoliosis to the

right. A cardiogram confirmed auricular fibrillation, and showed right ventricular preponderence.

He was given 2 c.c. of mersalyl intravenously, and oxygen by B.L.B. mask. On the night of admission, morphia, 1/4 of a grain, was given. One hour later the respirations became very shallow, and he died in five minutes.

Post-mortem examination. Heart weight, 490 g. Right ventricle greatly hypertrophied. Coronary arteries normal. Pulmonary artery atheromatous, with a circumference twice that of the aorta. Aorta normal. Lungs very œdematous, with diffuse emphysema.

Case 3. (Communicated by Dr. Macoun.) Male, aged 43. He complained of dyspnœa on exertion for eighteen months. He had a severe high right thoracic kyphoscoliosis which had not prevented him pursuing his occupation as gardener until shortly before admission, when the dyspnœa became so severe that he could not continue. He then had no evidence of congestive failure. Pulse rate 90, with ventricular extrasystoles. Blood pressure 140/100. Apex beat displaced four-and-a-half inches from the midline in the fourth intercostal space. Cardiac dullness to the right of the sternum. Heart sounds normal, and no murmurs. He was treated by rest in bed, mercurial diuretics, and theominal, and responded sufficiently well for him to be discharged to light work in four weeks. Four weeks later, he was precipitated into failure by a mild bronchitic attack. He was then moderately cyanosed. Pulse rate, 100, regular. Respirations 26. Temperature normal. Hepatic enlargement, and œdema of the ankles. Rhonchi heard over both lungs. Treatment again consisted of bed, rest, and mercurial diuretics, with some improvement. He was having restless nights, but in view of the experience of the first two cases, it was decided to give a small dose of morphia, 1/12 of a grain, before resorting to more usual dosage. The respirations became greatly depressed, and he died in one-and-a-quarter hours.

Post-mortem examination. Heart weight, 460 g. Right ventricular wall hypertrophied and dilated. Atheroma at origin of left anterior descending coronary artery. Circumference of pulmonary artery at upper level of valves, 8·2 cm. Circumference of aorta, 6·5 cm. No atheroma of pulmonary artery and only one small patch in aorta. Both lungs very small, with emphysema at borders. Bronchi congested and œdematous, typical of acute bronchitis.

Discussion

None of these patients had ever had morphia administered before the night of their death. The altered respirations and the times of death indicate that morphia probably played a part. Morphia has to be used with care in cyanosis, but it is common experience that, despite cyanosis, many cardiac patients react very favourably to its use. It is therefore reasonable to assume that severe kyphoscoliosis and the associated intrathoracic abnormalities have a bearing on this idiosyncrasy.

Trendelenberg (1926), remarking on morphine in kyphoscoliosis, stated: "Whereas, when the usual therapeutic amounts are given to people with unrestrained breathing, the crippling is usually shown only in a dulling of the breathing, and moderate diminution of breathing volume; in people with restrained breathing (dyspnœa following foreign body in the air passages, abnormal thoracic structure, etc.) even the usual therapeutic doses can so severely deteriorate the pulmonary ventilation through central effect on the breathing centre that life is threatened. In such cases, therefore, morphine should be used with the greatest care."

Chapman, Dill, and Graybiel describe the case of a girl, aged 29, with a severe high right kyphoscoliosis, who was given 1/3 of a grain of pantopon before an operation. Within a few minutes she became so cyanosed and dyspnœic that she had to be placed in an oxygen tent, and her condition remained critical for eight days.

Schroeder described an eclamptic patient whose respirations were depressed to between 2 and 3 a minute after the administration of 1/6 of a grain of morphia.

Severe kyphoscoliotic patients, even in the absence of cardiac failure, have greatly reduced vital capacities. In six such adult patients I have obtained values varying from 850 to 1850 c.c.

In the case of Chapman, Dill, and Graybiel, mentioned above, it was only 560 c.c. Once cardiac failure has supervened, the values will certainly be less. Any event that still further reduces pulmonary function, such as pulmonary infections, or the use of respiratory depresants, is quite sufficient to cause death. Cases 1 and 2, uncomplicated by infection, died after 1/4 of a grain of morphia. Case 3, complicated by infection, could not survive 1/12 of a grain. It is therefore suggested that morphia has no place in the treatment of heart failure consequent upon kyphoscoliosis.

Summary

Three cases are described of severe kyphoscoliosis and cardiac failure who died after the administration of morphia in small dosage. Reference is made to two cases, reported previously by others, who were precipitated into crises by respiratory depresants.

My thanks are due to Sir Maurice Cassidy for permission to publish Cases 1 and 2, and to Dr. Stephen Macoun for the details of Case 3.

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TRANSIENT HEART BLOCK AND CORONARY OCCLUSION IN PLEURAL SHOCK

BY

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Pleural shock is, happily, a rare accident. Anderson (1936) estimates that it occurs once in 2000 refills, and that the fatality rate may vary from 15 to 50 per cent. Ormond (1942), reviewing the reported cases, considers it less common. Be that as it may, it is an alarming happening.

This case, in which syncope occurred during an attempted artificial pneumothorax induction, has unusual features; and some explanation of what occurred will be attempted, though no final conclusions can be drawn.

Case Notes

An attempt was made to induce an artificial pneumothorax in a woman of 24 with tuberculous infiltration of the left upper lobe. The two layers of pleura were found to be adherent, so the attempt was abandoned and she was returned to the ward. A few minutes later she complained of faintness and difficulty in breathing; she became pale, cold, and clammy, with cyanosed lips and dilated pupils; and soon she was unconscious. The respirations were deep and sighing, and the neck veins moderately distended; the pulse could not be felt at the wrist and auscultation showed a slow heart rate. Fig. 1A, taken at this stage, showed complete heart block with a ventricular rate of 44. Atropine sulph., 1/100 of a grain, was given intravenously, and the pulse rate increased in four minutes to 120 a minute. After fifteen minutes Fig. 1B showed normal rhythm at a rate of 65 a minute. Clinical improvement quickly followed the increase in her pulse rate. She soon regained consciousness and in about an hour she seemed reasonably well again. At no time, then or later, did she complain of pain. Five weeks later another electrocardiogram was taken: this, surprisingly, showed strong evidence of a T I type of coronary occlusion. Subsequent records were typical of what might be expected in the gradual return of a coronary curve towards normal. Five months after her attack, she was transferred to a sanatorium in another part of the county with a view to thoracoplasty, but this was not done, and she has since died of pulmonary tuberculosis. This, therefore, seems to be an example of pleural shock with subsequent coronary damage.

Discussion

Pleural Shock. This has been attributed either to a vagal reflex or to air embolism. Opinions differ as to which is the more common and important cause. Cocke (1931, 1935), for instance, considers that it is most commonly a reflex syncope, while Rukstinat (1931) believes that the symptoms are generally the result of air embolism. Forbes (1944), quoting Hamilton and Rothstein, and Chase, in support of his opinion, agrees with Rukstinat. It is evident, however, as Ormond (1942) concludes, that there are two forms of pleural shock—one being a reflex syncope and the other due to air embolism. The former appears to resemble, clinically, an ordinary fainting attack such as has been discussed recently in blood donor clinics. (M.R.C. Report, 1944). That the latter does occur there can be no doubt, the evidence being the cases that have been reported with cerebral symptoms and hemiplegia,

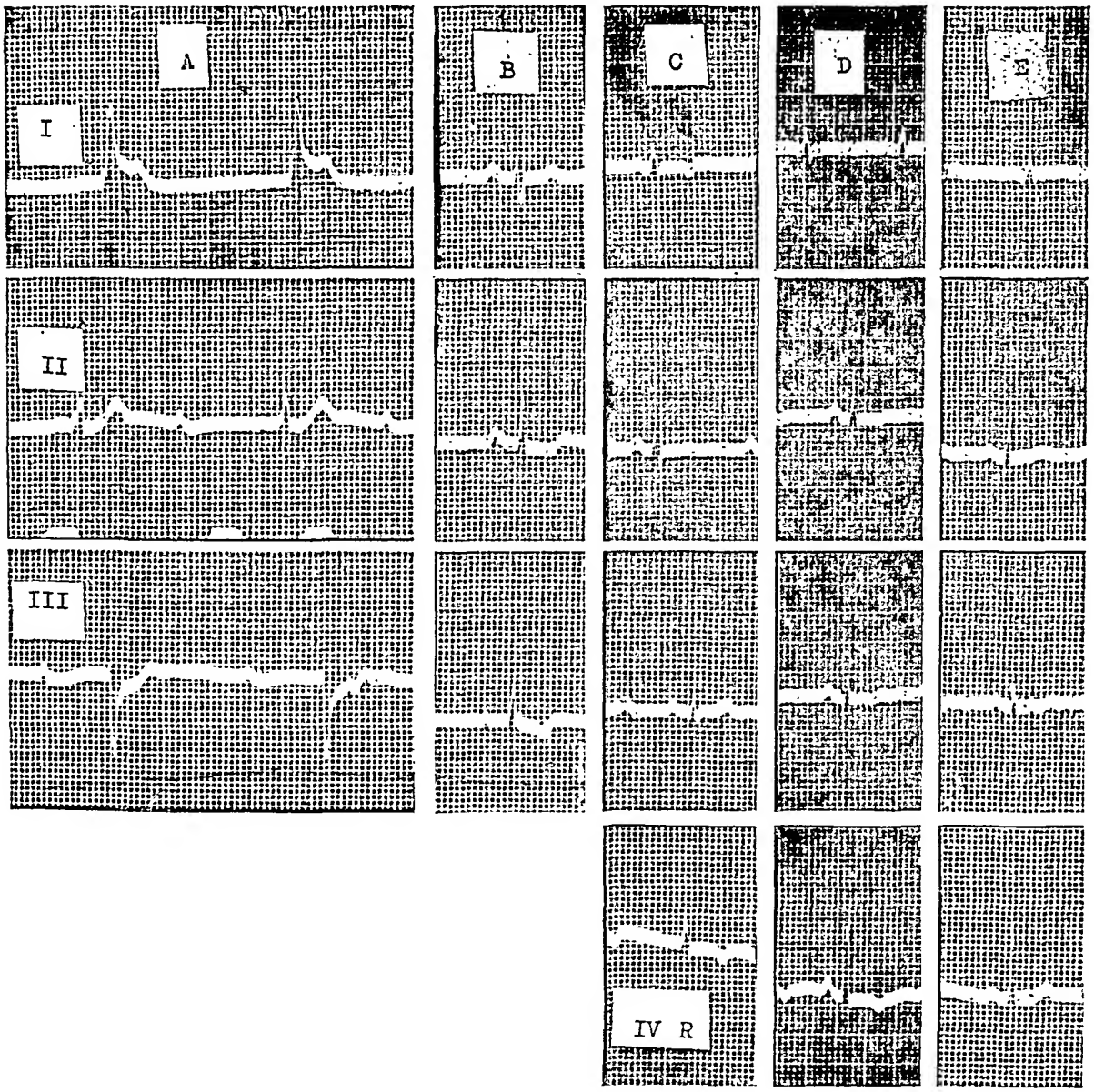

FIG. 1.

(A) 19/6/44. Complete heart block, ventricular rate 44, auricular rate 98. Bizarre QRS–T complex in leads I and III. QRS II, 0·08 sec., S–T II depressed 0·5 mm., T positive, 3·5 mm. (B) 19/6/44, fifteen minutes later. Resumption of normal rhythm, rate 65; P–R interval, 0·2 sec.; right axis deviation, and T III inverted. (C) 28/7/44. Development indicating occlusion of anterior coronary, T I, type. (D) 12/9/44. Regression. T I now flat, T IV still inverted. (E) 17/10/44. T I and T IV now upright, low voltage in limb leads.

the post-mortem demonstration of air in the cerebral and, sometimes, in the coronary arteries, and the clinical signs of air embolism occasionally seen during life in the retinal arteries.

Complete Heart Block. This is most often due to an intrinsic myocardial lesion (Parkinson, Papp, and Evans, 1941), though rarely, as described by Weiss and Ferris (1934), it may be reflex. Comeau (1937), discussing paroxysmal complete block, attributes most cases to coronary sclerosis. There may, again, be a contributory vagal factor as well as a basis of sclerosis, as in Starling's (1921) case which Comeau quotes; here Stokes-Adams seizures were arrested by atropine.

It is possible, therefore, that in my case, as normal rhythm was quickly restored after atropine, some vagal factor was present; yet it must be admitted that normal rhythm might have been resumed in any case.

It is well known (Katz 1941, and others), that complete heart block may mark the onset of

an acute coronary occlusion. It is doubtful whether atropine would restore normal rhythm in those circumstances.

Coronary Embolism. The great majority of acute coronary occlusions must be due to thrombosis. A number of cases caused by various emboli has been collected and extended by Porter and Vaughan (1940). No mention of air embolism is made. In all the cases they describe, præcordial pain was a feature, and a cardiogram of one of them shows a T I type of coronary curve.

Durant (1934), however, describes a probable case of coronary air embolism, with cardiographic evidence of a T I type of coronary occlusion. Here some complaint of substernal oppression was made, but syncope and a generalized convulsion were the most prominent features.

Summary

In the case here described, heart block existing during the acute phase may have been due partly to a vagal reflex, yet a more important factor, from the subsequent cardiogram would appear to have been a coronary occlusion. The possibility of acute coronary insufficiency without occlusion, as described by Master (1944), is not a likely one; his cardiograms do not resemble those here described. It is hardly likely that a coincident coronary thrombosis took place. The close association with the attempted pneumothorax induction, together with the age of the patient, make this extremely unlikely. A wound of the heart can be excluded: the needle was never deep enough to have produced this. A clot disturbed from a thrombotic process in the pulmonary circulations might produce an embolism (Saphir, 1933) and this remains a possibility. It seems more reasonable to assume that an air embolism occurred.

Fig. 1B shows, curiously, right axis deviation, without a coronary type of curve. As the typical changes indicative of coronary occlusion may take some little time to develop—up to a few hours (White, 1931)—this right axis deviation may have existed before the accident, as in Durant's case. Fig. 1C, D, and E leave little doubt that recovery was taking place from myocardial infarction.

An interesting point is the absence of pain. Pain is evidently not one of the main features of this form of pleural shock. It may be that this absence of pain is a clinical characteristic of coronary air embolism, in contradistinction to other types of occlusion.

Heart block may occur more commonly in pleural shock than is thought, and Cocke remarks on bradycardia in two of his cases.

It is suggested that in the case here reported, coronary air embolism occurred producing transient heart block and myocardial infarction.

I have to thank Dr. John Parkinson for many helpful suggestions about this case.

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PAROXYSMAL TACHYCARDIA IN INFANCY AND CHILDHOOD

BY

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Occasionally in pædiatric wards and more often in private practice, one learns of cases of sudden death in infants and children. The clinical signs have not been characteristic for a diagnosis, and the autopsy has failed to determine the cause of death. Among these there are a number whose sudden death is due to paroxysmal tachycardia. Its occurrence has been considered rare in infancy and childhood, but is more frequent among children than is commonly thought. Of recent years, the number of case reports has been increasing, due to the greater interest taken in the cardiovascular diseases in childhood.

Apart from reports of isolated cases, there are only three papers dealing with more than one case. Koplik (1917) reported three cases: the first was a baby of 22 months, who had tonsillitis and bronchitis two weeks before the onset of paroxysmal tachycardia; the second was a child three years of age, and the third a child ten years old; in the last case the paroxysmal tachycardia started after a tonsillar sepsis and the attacks were observed for two years. Shookhoff *et al.* (1932) reported four cases: the paroxysms occurred in a child of eight with septic teeth; in a child of three after pertussis; in a child aged ten with an abscess of the right lower premolar and pharyngitis; and in another case three years of age. Campbell (1937) added three cases in the *Guy's Hospital Reports*: the first was a baby one month old with a temperature 101° F., but with no other definite pathological findings; the second a baby of 20 months with vomiting and liver enlargement; and in the third paroxysmal tachycardia manifested itself in a child of three years with bronchitis of two weeks standing and with otitis media. Hubbard (1941) called attention to the fact that paroxysmal tachycardia shows itself as a distinctive clinical entity in young infants, responding satisfactorily to proper treatment; he reported nine cases in infants less than one year of age.

Considering the paucity of reports on this subject it seems justifiable to give an account of the cases observed in this hospital from 1941 to 1945. It comprises eleven cases; a short clinical report, cardiographic findings, pathological, anatomical, and histological reports are given below.

Clinical signs. The onset of paroxysmal tachycardia is sudden. The attack lasts for minutes, hours, or days. The child appears acutely ill on physical examination. It is restless at the outset, but apathetic once the attack is developed, and looks pale and often cyanosed. There is respiratory distress with rapid and shallow respirations. During the attack, most commonly the heart rate is 160–200 a minute, but rates of 270 and 300 have been observed (Campbell, Langley, Lewis, Werley). Between and following attacks premature beats are often found. Signs of congestive heart failure, e.g. râles in the lungs, engorged jugular veins, and liver enlargement may develop. The pulse is often imperceptible. The temperature is usually raised. The X-ray shows pulmonary congestion and an enlarged heart in some instances.

A heart rate exceeding 190–200 in a small infant should always rouse suspicion. Too little attention is paid to a rapid heart action in babies, and that is the reason for paroxysmal tachycardia being sometimes overlooked.

Case Reports

Case 1. Three years old, admitted 13/12/1941. No previous diseases. Clinical diagnosis: nasopharyngeal diphtheria of gravis type. 60,000 units antitoxin given intraperitoneally. Heart on admission: cardiac dullness enlarged, embryocardia. The next day there was restlessness and cyanosis, and the paroxysm started (Fig. 1). The patient died the same day.

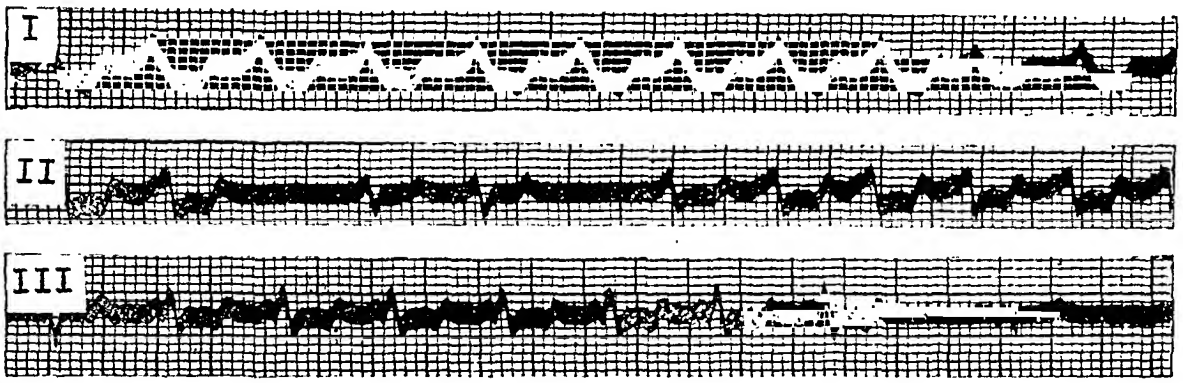

Fig. 1.—Case 1. 14/12/41. Ventricular rate 155 a minute; duration of QRS, 0·07 sec.; P–R, 0·05 sec. in lead III. This supraventricular tachycardia is considered to be of upper nodal origin.

Case 2. Four years old. Admitted 27/12/1941. Previous diseases: pertussis, chicken-pox, mastoid operation. Diphtheria two weeks ago. Clinical diagnosis: diphtheritic myocarditis. Heart on admission: enlarged cardiac dullness, systolic apical murmur. Second apical sound accentuated, pulse 108 a minute.

29/12/41. Onset of heart paroxysm (Fig. 2A), cyanosis, liver enlargement; albuminuria.

31/12/41. Heart action irregular due to premature beats.

1/1/42. Pulse 138. Extrasystoles. B.P. 76–48 (see Fig. 2B).

8/1/42. Heart action regular. Colour fair. Liver not enlarged, albuminuria subsiding. No murmur audible.

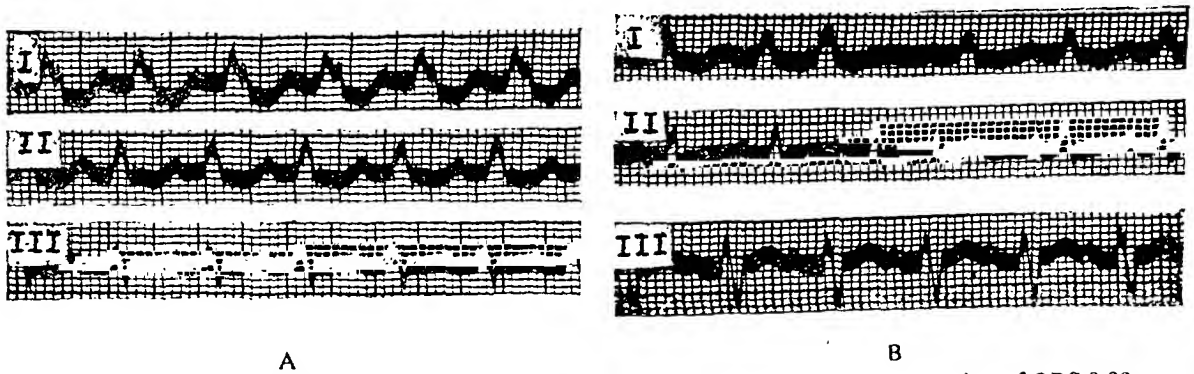

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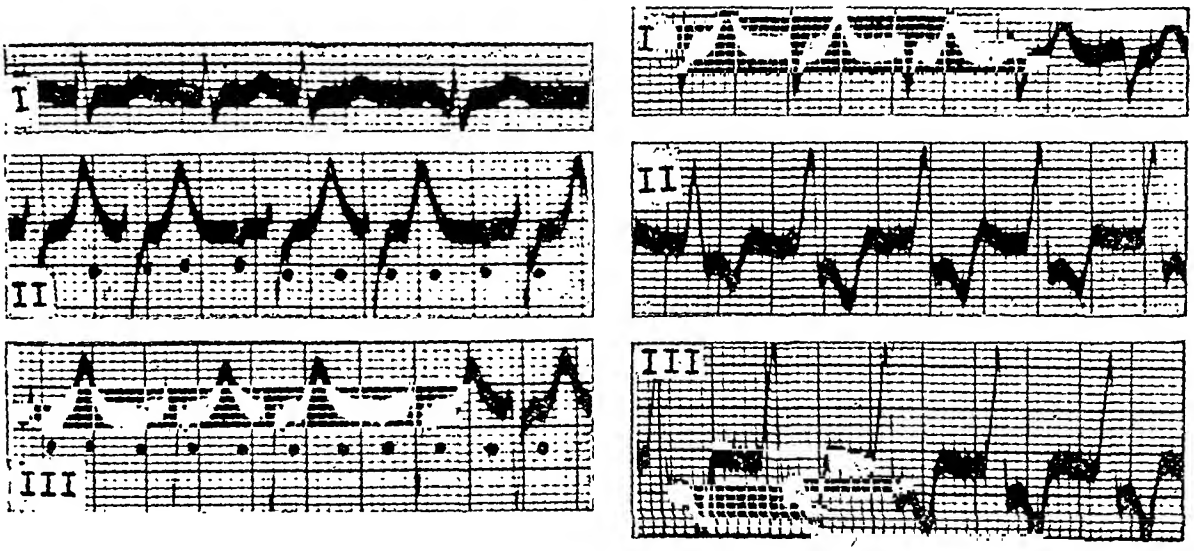
Fig. 2.—Case 2. (A) 29/12/41. Heart action regular, ventricular rate 150 a minute, duration of QRS 0·08 sec. Supraventricular paroxysmal tachycardia. (B) 2/1/42. Sinus rhythm, ventricular rate 130 a minute; P–R, 0·17 sec. Premature beats. T flat in leads I and II. Ventricular deflections notched, voltage less than 1·5 mV. in all three leads.

Case 3. Six years old. Admitted 4/5/1942. No previous diseases. Clinical diagnosis: nasopharyngeal diphtheria of gravis type. 60,000 units antitoxin intraperitoneally. Heart normal on admission.

6/5/42. Pale and apathetic, with vomiting and an imperceptible pulse (see Fig. 3A).

7/5/42. Cardiac dullness enlarged, vomiting persistent. Attack persisted but was thought to be paroxysmal ventricular tachycardia (see Fig. 3B). The patient died two days later.

Case 4. Five years old. Admitted 14/4/1943. Previous diseases: measles. Clinical diagnosis: hæmorrhagic nasopharyngeal diphtheria of gravis type. 60,000 units antitoxin given intravenously. Blood transfusion. Heart normal on admission. B.P. 80/53.



A B

FIG. 3.—Case 3. (A) 6/5/42. Action irregular. Alternately every second and third P wave hidden within the T wave. Auricular tachycardia with 3:1 and 2:1 A-V block; A, 300; V, 130. In this and in other figures dots designate P waves. (B) 7/5/42. Action regular. Ventricular rate 140 a minute. Duration of QRS 0·10 sec. Atypical configuration of the ventricular deflection. Ventricular paroxysmal tachycardia.

18/4/42. Pale; cardiac dullness enlarged. Pulse 100. B.P. 66/42.
21/4/42. Apathetic, vomiting. Pulse 100–90 a minute.
24/4/42. Cyanosis, restlessness. Heart rate 88. Premature beats.
24/4/42. Onset of heart paroxysm, pulse imperceptible. B.P. ?38/20 (see Fig. 4). The patient died two days later.

Case 5. Four years old. Admitted 11/4/1944. Previous diseases: chickenpox. Clinical

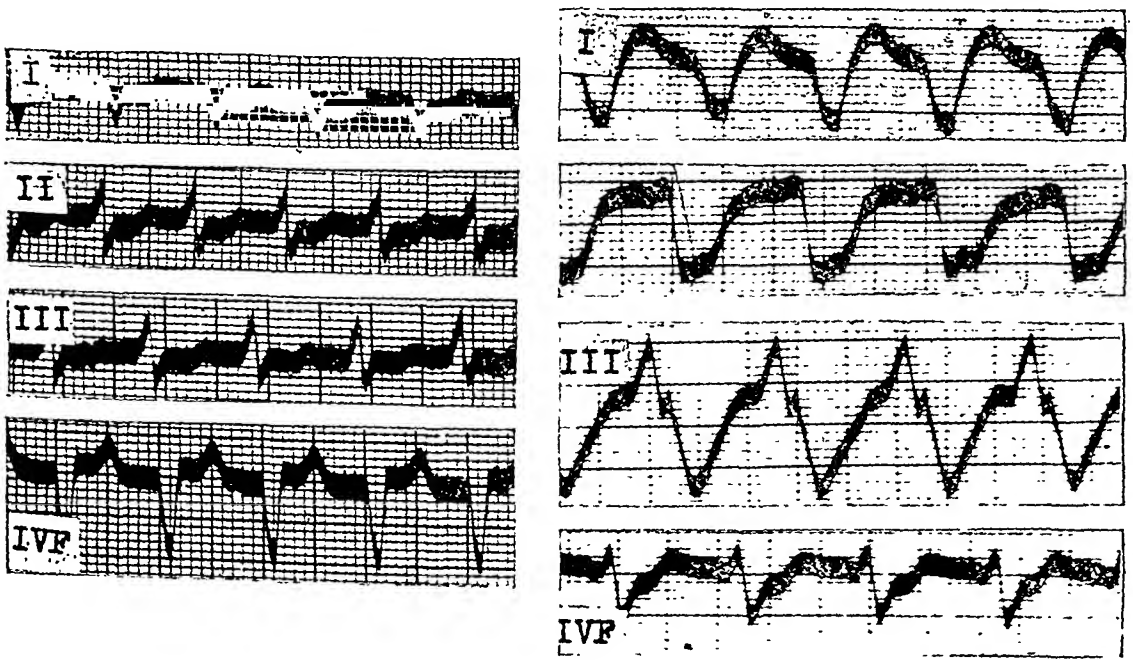


FIG. 4.—Case 4. 24/4/42. Heart action regular. Ventricular rate 160 a minute. Duration of QRS 0·08 sec. Since no P waves are visible, this supraventricular tachycardia is considered to be of nodal origin.

FIG. 5.—Case 5. 15/5/44. Heart action regular. Ventricular rate 120. Ventricular complexes bizarre; duration 0·23 sec. Ventricular paroxysmal tachycardia.

diagnosis: nasopharyngeal diphtheria of gravis type. 80,000 units antitoxin given intravenously. Heart normal on admission.

15/5/44. Onset of heart paroxysm (Fig. 5). Vomiting; pulse imperceptible; respiratory rate 20; albuminuria. Died.

Case 6. Five years old. Admitted 5/5/1944. Previous diseases: ?diphtheria, measles, otorrhœa. Clinical diagnosis: nasopharyngeal diphtheria of intermedius type. 40,000 units antitoxin given intramuscularly. Pulse rate 130–140. First and second sounds equal; B.P. 110/80.

11/5/44. Second apical sound greater than first. Pulse 100–108. Albuminuria.

12/5/44. Pallor, vomiting, temperature normal. Onset of heart paroxysm (Fig. 6). Died.

Case 7. Six months old. Admitted 20/6/1944. Previous diseases: bronchitis, eczema, measles a week ago. Clinical diagnosis; pertussis. Heart normal on admission. W.B.C., 56,000; 68 per cent lymphotcytes.

19/7/1944. Syncope, cyanosis. Pulse imperceptible (Fig. 7). No clinical signs of pneumonia (Fig. 7).

20/7/1944. Extreme tachycardia and tachypnœa. Temperature raised. Signs of heart failure, râles in the lungs. Died.

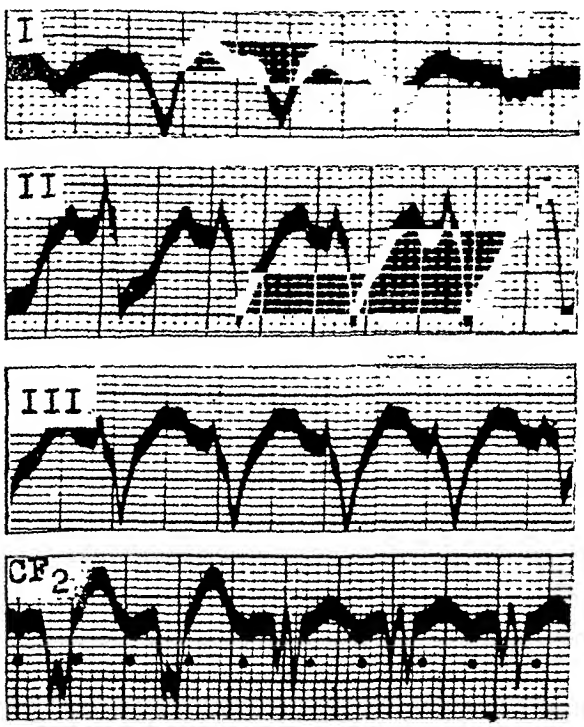


FIG. 6.—Case 6. 12/5/44. Action regular in lead II and III. Ventricular rate 143. Duration of QRS 0·12 sec. Auricular waves thought to be visible in chest lead CF_2, auricular rate 272, every second P wave hidden in the following T wave. Auricular paroxysmal tachycardia with 2:1 A-V block.

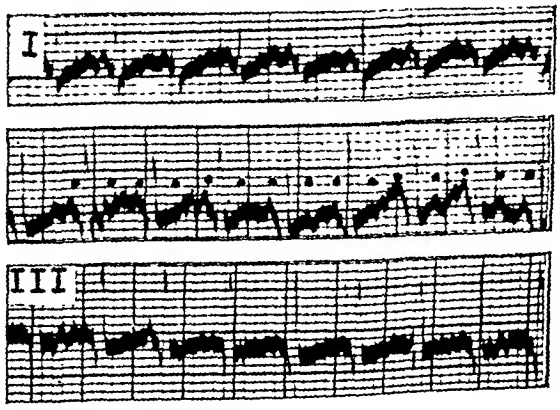


FIG. 7.—Case 7. 19/7/44. Heart action regular. Auricular paroxysmal tachycardia with possible 2:1 conduction : A, 460; V, 230.

Post-mortem report. (From the Department of Pathology, University of Durham.)

Pericardium, smooth and glistening. Heart, 52·0 g. (Mean weight at this age 31·0 g.) Epicardium quite smooth. Right auricle dilated and filled with agonal clot; no thrombus in appendix. Foramen ovale completely closed. Tricuspid leaflets thin and delicate. Right ventricle slightly dilated; wall 0·3 cm. thick. Pulmonary valves thin and delicate. Pulmonary artery smooth and elastic. Left auricle empty; no evident dilatation; no thrombus in appendix or elsewhere. Mitral leaflets thin and delicate. On anterior leaflet 0·2 cm. from the free margin there is an " angioma "; about 0·2 cm. from it is another one which appears to have

healed. Left ventricle not dilated; very little clot; wall 0·7 cm. thick. Aortic leaflets thin and delicate. Orifices of coronary arteries patent. Ductus arteriosus closed. Aorta smooth and elastic. Myocardium firm but greyish and pink.

Histology. A topographical survey of the heart, including epicardium, right and left auricles, mitral and tricuspid valves, annulus fibrosus, auriculo-ventricular sulcus, right and left ventricles, was made and there was no trace of any form of myocarditis. Special staining showed a mild grade of diffuse fatty degeneration of the myocardium which could be due to many forms of toxæmia.

Case 8. Three years old. Admitted 18/10/1944. Previous diseases: rubella, pertussis. Clinical diagnosis; hæmorrhagic nasopharyngeal diphtheria and *S. hæmolyticus* infection. 50,000 units antitoxin intravenously. Blood transfusion. Heart normal on admission.

21/10/44. Runs of premature beats and short paroxysm (Fig. 8A). B.P. 85/38. Albuminuria.

24/10/44. Onset of longer paroxysm. Pulse too fast to count (Fig. 8B).

26/10/44. Extremities icy-cold. Liver enlargement. B.P. could not be measured. Patient died.

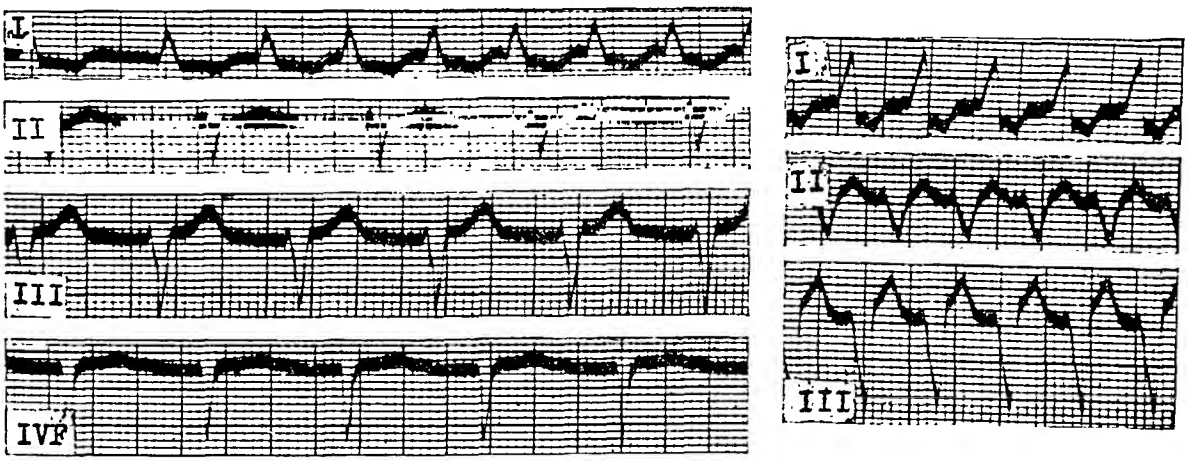


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FIG. 8.—Case 8. (A) 21/10/44. Onset of supraventricular paroxysmal tachycardia in lead I. Ventricular rate 171. The paroxysm has subsided in lead II, the rate being 82. There are no P waves visible, the heart action is regular especially in lead III, in which the ventricular rate is 100. Duration of QRS 0·10 sec. The paroxysm in lead I and the rhythm in lead II and III are considered to be of nodal origin. (B) 24/10/44. Heart action regular. Ventricular rate 188, duration of QRS 0·11 sec. Left ventricular preponderance. Ventricular paroxysmal tachycardia.

Post-mortem report. (From the Department of Pathology, University of Durham.)

Heart. Weight 90 g. (fixed in formalin). Right auricle slightly dilated, containing a large amount of post-mortem thrombus. Auricular appendage contains adherent mural thrombus. Foramen ovale closed. Tricuspid valve admits two fingers: cusps thin and delicate. Right ventricle slightly dilated and contains post-mortem thrombus. Endocardium shows hæmoglobin staining; muscle, 0·3 cm. thick at the base. Pulmonary valve shows marked hæmoglobin staining of its cusps. Coronary artery normal apart from hæmoglobin staining. Left auricle healthy: no mural thrombi. Mitral valve admits one finger and cusps thin and delicate. Left ventricle dilated with some endothelial hæmorrhages on the interventricular septum: muscle at the base 0·7 cm. thick. Aortic valve healthy. Coronary arteries patent. Myocardium, no obvious fatty change.

Histology. Heart: left auricle, mitral valve, left ventricle. Intense veno-capillary congestion in the myocardm together with a sparsely but widely distributed fatty degeneration. No evidence of myocarditis or valvulitis.

Right auricle, tricuspid valve, right ventricle. Recent mural ante-mortem thrombus in appendix, but apart from this changes similar to those in the left side.

Auriculo-ventricular node; similar changes but no inflammation.

The appearance here pointed to an acute and intense cardiac failure, the cause of which is not apparent from this material.

Case 9. Four years old. Admitted 1/12/44. No previous diseases. Clinical diagnosis: meningo-encephalitis. Heart normal on admission, no consolidation in the lung. W.B.C., 16,800; 74 per cent polymorphs and 21 per cent lymphocytes.

7/12/44. Pulse 124. B.P. 105/65. Lung: no apparent disease.

9/12/44. Onset of heart paroxysm, pulse too fast to count (Fig. 9). Temperature 100° F., signs of consolidation in the lung. Died.

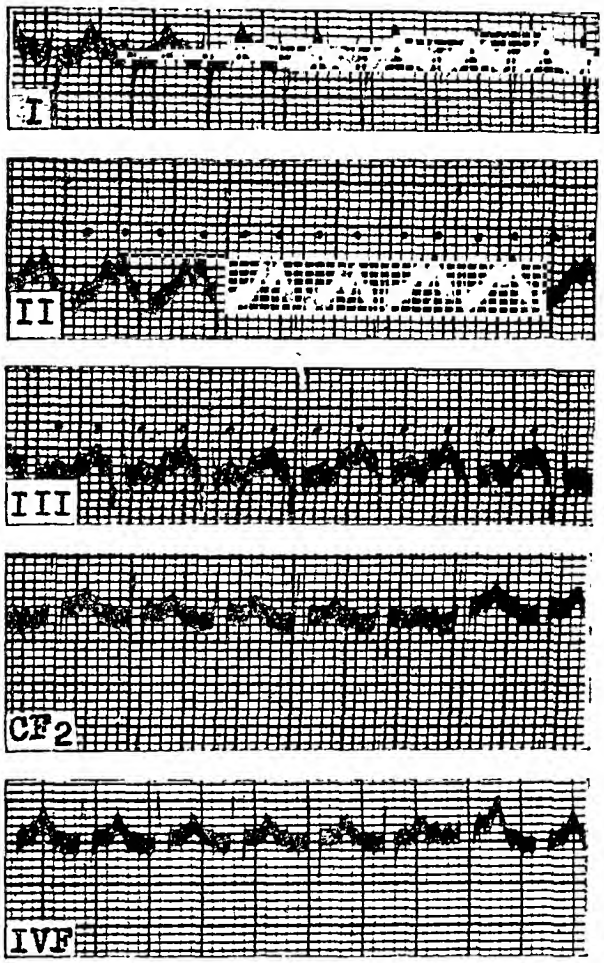

FIG. 9.—Case 9. 9/12/44. Heart action regular. Auricular rate 376, ventricular rate 188. Alternate P waves hidden within the S–T transition. Paroxysmal auricular tachycardia with 2:1 A-V block.

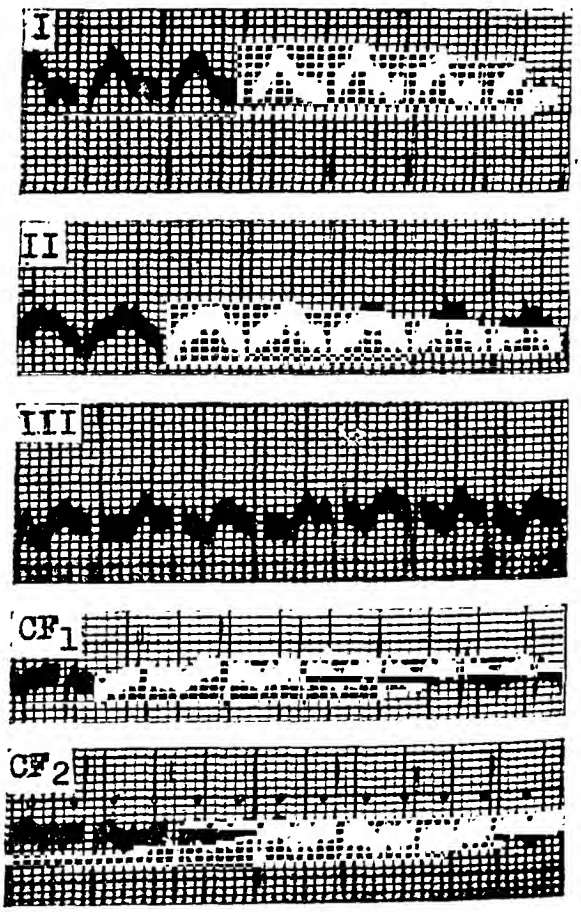

FIG. 10.—Case 10. 18/2/45. Action regular. Ventricular rate 176. Auricular rate 352. Both auricular waves are hidden within the S–T–T complex. Paroxysmal auricular tachycardia or flutter with 2:1 A-V block.

Post-mortem report. (From the Department of Pathology, University of Durham.)

Anatomical diagnosis: Acute suppurative meningitis. Acute bronchopneumonia. Accidental involution (thymus).

Pericardial sac, smooth and glistening.

Thoracic aorta, quite smooth and elastic.

Heart. Weight 75 g. (fixed in formalin). Pericardium smooth and glistening: no gross abnormality. Right auricle empty. Foramen ovale completely closed. Tricuspid leaflets thin and delicate. Right ventricle a small amount of post-mortem clot: wall 0·3 cm. thick. Pulmonary valves thin and delicate. Pulmonary artery smooth and elastic. Left auricle empty. Mitral leaflets thin and delicate. Left auricle empty, but dilated: wall 0·9 cm. thick. Pulmonary leaflets thin and delicate. Orifices of coronary arteries patent. Myocardium distinctly pale and turbid in appearance.

Histology. Heart (left auricle, myocardium, left ventricle): no evident abnormality.

Case 10. Four months old. Admitted 13/2/45. Previous diseases: otorrhœa. Clinical diagnosis: epidemic cerebrospinal meningitis. Heart on admission: tachycardia. Pulse volume poor.

17/2/45. Slight vomiting. B.P. 98/40. W.B.C.: 24,000; 61 per cent polymorphs and 25 per cent lymphocytes.

18/2/45. Onset of heart paroxysm (Fig. 10).

20/2/45. Heart action regular, rate 150 a minute.

22/2/45. Cardiac dullness enlarged, pulse volume good.

1/3/35. Heart: no apparent disease.

Case 11. Five months old. Admitted 15/2/45. No previous diseases. Has been ill for the last five days, but no clinical signs could be found. The baby's mother had a sore throat a few weeks ago, and a child in the same family got scarlet fever two weeks ago; because of this the baby was given scarlet antitoxin and sulphonamide before admission. Heart on admis-

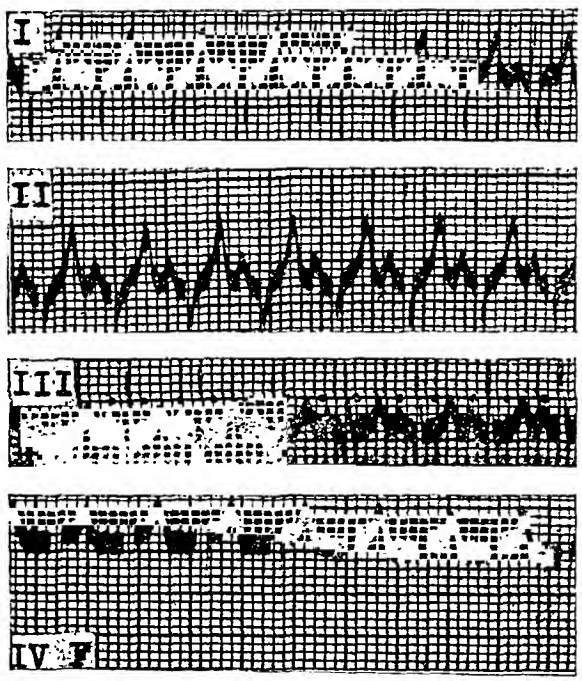

FIG. 11.—Case 11. 15/2/45. Heart action regular. Ventricular rate 222, auricular rate 444. Paroxysmal auricular tachycardia with 2:1 A-V block.

sion: action too fast to count. Lung: no apparent disease. Clinical examination did not reveal any signs of a *S. hæmolyticus* infection.

16/2/45. Colour grey, eyes sunken, hands cold. Lung: no consolidation: X-ray negative. Bacteriological findings negative. Patient died.

DISCUSSION

Eleven cases of paroxysmal tachycardia are reported in the present series. The age of the patients was under one year in 3 cases, and from three to six years in 8 cases.

The heart condition was associated with various infections: a diphtheritic infection of gravis or intermedius type was present in seven cases, pertussis was found in another, meningitis in two more, but no infectious focus could be traced in the last case, a baby five months old. These findings leave little doubt that paroxysmal tachycardia in childhood occurs more often in the presence of an infection than in its absence. Koplik assumed that the first attack of influenza in one of his cases was the starting point of the paroxysm, and that the cardiac collapse of the first paroxysm was the forerunner of the subsequent paroxysms. The infective origin is obvious in Shookhoff's cases, e.g. in one child while convalescing from pertussis. Hauser (1921) referred to pertussis as a cause of paroxysmal tachycardia. Hubbard admits

that paroxysmal tachycardia may be associated with some other illness, but he believes it may start with no other evident cause. One child in Campbell's series probably had a diphtheria prior to the onset of the paroxysmal tachycardia.

The attack sets in suddenly. There are runs of premature beats lasting for a few seconds, heralding the onset of the paroxysm in some instances (see Fig. 8A). Frequent premature beats may also occur when the attack terminates (see Fig. 2B).

The main clinical signs enumerated in order of their frequency in the present series are the following: imperceptible pulse (6 cases), lowered systolic and diastolic blood pressure (5), vomiting (4), cyanosis (4), albuminuria (4), enlarged cardiac dullness (4), pallor (3), liver enlargment (2), apathy (2), raised temperature (2), syncope (1), embryocardia (1), systolic apical murmur (1), râles in the lung (1), and restlessness (1).

There are two cases in the present series which are of the type described by Hubbard (Cases 7 and 11), occurring in babies of six months and of five months. Pallor, restlessness, raised temperature, and the paroxysm being the signs of the onset, followed by signs of a failing heart the next day. No consolidation in the lung is found on clinical or X-ray examination. Attacks similar to those described might be mistaken for pneumonia; tachypnœa, cyanosis, and a raised temperature readily suggest a diagnosis of pneumonia.

Cardiographic findings. Auricular paroxysmal tachycardia and auricular flutter are closely related. Campbell found paroxysmal flutter to be more frequent in infants than in adults, and he regarded it as more common in infants than all varieties of simple paroxysmal tachycardia combined. Koplik's Case 3 was an example of auricular flutter. Three out of four cases of paroxysmal tachycardia reported by Shookhoff were auricular flutter. He gives a review of 40 cases of paroxysmal tachycardia occurring in children and published by different authors up to 1932. These cases presented themselves as ventricular paroxysmal tachycardia, 1 instance; auricular paroxysmal tachycardia, 5 instances; nodal paroxysmal tachycardia, 2 instances; paroxysmal auricular flutter, 12 instances; undiagnosed paroxysmal tachycardia with a rate of 200 or more, 18 instances.

Campbell regarded his Case 3 as probably flutter with 1:1 response. Up to-day it has been held that paroxysmal tachycardia is found with an auricular rate varying between 160 to 240, while auricular flutter is associated with higher auricular rates of about 300 a minute. Furthermore it was thought that auriculo-ventricular block is characteristic of auricular flutter, but was considered uncommon in paroxysmal tachycardia. This no longer holds good as A-V block is found in auricular tachycardia as well (Barker *et al.*, 1943; Decherd *et al.*, 1943; and Evans, 1944). It was found in two instances (Cases 3 and 6) in the present series. Chest leads proved to be more reliable in demonstrating auricular activity than the limb leads. In our experience chest leads are more useful in the examination of adults than of babies and infants. The comparatively small size of the heart and chest wall in this early age of life seems to be the reason for the difficulty in applying an electrode to a selected area of the heart. Fig. 6 shows that a chest lead might reveal auricular activity while there are no certain signs of auricular activity in the limb leads. In most cases, however, the limb leads in babies and infants show the auricular waves as well or in some instances even better than the chest leads. Lewis (1912) and Carr (1932) found that paroxysmal tachycardia may change into auricular flutter, which suggests some relationship.

Ventricular paroxysmal tachycardia. There were three records in the present series. The duration of QRS is prolonged, and QRS is not accompanied by P waves. The configuration of the ventricular deflections is such that it may be difficult to distinguish the QRS from the S–T–T.

Nodal paroxysmal tachycardia. Three records were found in the present series. The ventricular rate varies between 150 to 160 a minute.

Sinus tachycardia is readily distinguished from paroxysmal tachycardia by the presence of P waves and a normal P–R interval which may normally be of 0·08 sec. duration in babies and infants.

Pathological anatomy and histology. It is remarkable that distinctive pathological changes either in the myocardium or in the conductive tissue have not been found in three cases of the present series, where an autopsy was performed. Two were cases of paroxysmal auricular

tachycardia or flutter with 2:1 block, one of paroxysmal ventricular tachycardia. The pathological findings in these three showed no evident abnormality, no trace of myocarditis or valvulitis, though the appearances pointed to an acute and intense cardiac failure in one instance. This is of great practical importance; it is obvious that paroxysmal tachycardia has to be diagnosed during life or it will not be diagnosed at all, the post-mortem examination showing no pathological changes.

The prognosis is grave in infants and very grave in cases in which the underlying infection is severe, e.g. in diphtheria of gravis type. In milder cases, the attack may stop spontaneously.

Treatment. Digitalis given promptly may have an effect in some instances, and save the child's life. Koplik had this impression in one of his cases. Hubbard reports very good results. The treatment with digitalis had no chance in the diphtheria cases of the present series. In only one (Case 2) was the result satisfactory. In a case of meningitis (Case 10), flutter was changed into fibrillation and this came under control by digitalis treatment. The results with other drugs recommended for treatment of paroxysmal tachycardia, e.g. quinidine and magnesium sulphate intravenously are also not always satisfactory. Further, it was found that pressing on the carotid sinus or the eyeball, which may stop an attack in an adult, were not effective in infants.

This report gives a rather poor prognosis for paroxysmal tachycardia in infancy and childhood. It must not be forgotten, however, these investigations were carried out on children admitted with or suspected of severe acute infective diseases. Where a mild infection may have been the causative factor the response to treatment, and thus the prognosis is probably much better.

SUMMARY

Paroxysmal tachycardia occurs more often in infancy and childhood than is commonly thought, and it accounts for some instances of sudden and unexplained death in infancy.

Clinical and cardiographic signs of eleven cases and pathological anatomical and histological findings of three autopsies are reported.

Prognosis and treatment are discussed.

It is with kind permission of Professor A. F. Bernard Shaw, Department of Pathology, University of Durham, that the post-mortem notes are included with the present report.

I wish to thank Dr. McCracken, M.O.H., Newcastle-upon-Tyne and Dr. E. F. Dawson-Walker, former Medical Superintendent of the City Hospital for Infectious Diseases, Walkergate, for facilities granted.

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TRAUMATIC RUPTURE OF THE INTERVENTRICULAR SEPTUM

BY

TERENCE EAST

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The results of damage to the heart from indirect violence have aroused a good deal of interest in recent years, for in many cases modern methods of investigation have increased the possibilities of diagnosis. The account of this unusual case seems worthy of record.

A young man of nineteen years had a head-on collision with a lorry when driving a motor car. He was thrown forcibly against the steering wheel and hurt the front of his chest. Breathing was rather painful, but no bones were broken. He was in hospital for a fortnight. No cardiac murmur was noted. On returning home later he was examined by his family doctor and a murmur was heard. He was then referred for further examination. Three months before the accident he had been passed by a medical board for the R.A.F.

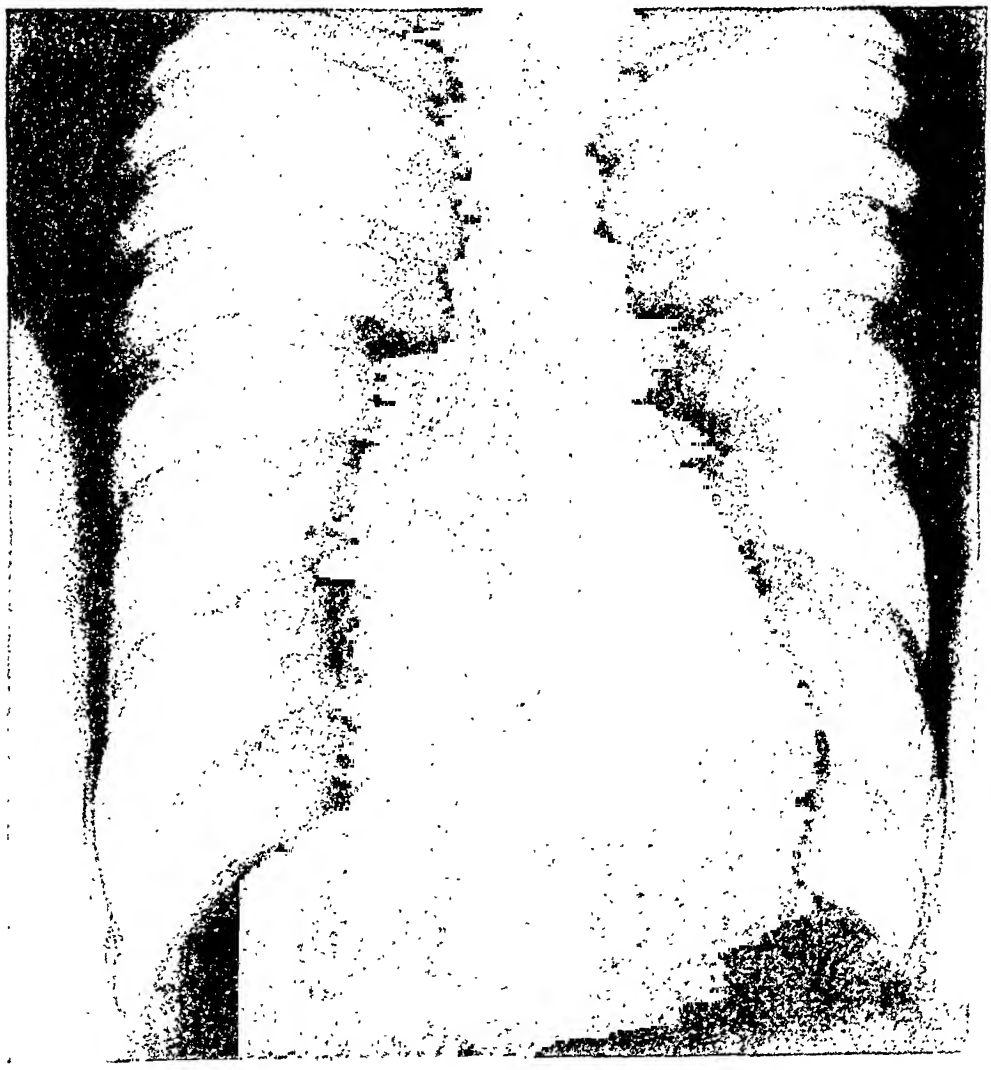

FIG. 1.—Teleradiogram of the heart, showing no abnormality except a little enlargement to the right.

The patient was a tall thin youth with rather a flat chest, somewhat depressed just to the left of the sternum. The apex beat was in the fifth left space, four and a half inches to the left of the mid-line. It was rather increased in force and rate from nervousness. An intense rough systolic murmur was audible all over the præcordium, loudest about the left edge of the sternum in the fourth left intercostal space. It was not conducted in any particular direction. A strong systolic thrill accompanied the murmur. The mitral first sound was faintly reduplicated until the rate slowed down; a faint third sound followed the mitral second, but only on acceleration. The pulmonary second sound was rather loud. The

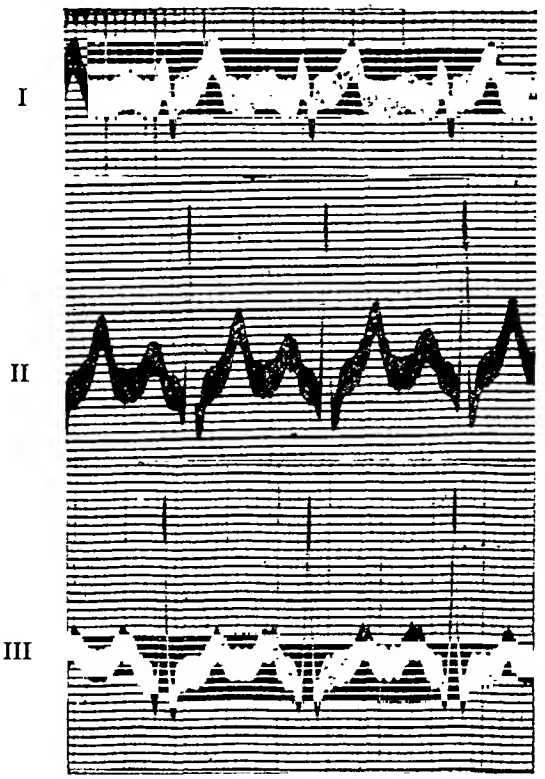

FIG. 2.—Electrocardiogram, showing some right axis deviation.

blood pressure was 140/90. There was no dullness to the right of the sternum. There was no cyanosis, nor engorgement of the jugular veins or liver. He had no symptoms. At the time it was not possible to take a cardiogram or a skiagram.

Three and a half years later he was seen again. He had had no symptoms and was following a quiet occupation in a technical laboratory. The physical signs had not changed at all. The blood pressure was 120/80. Screening showed that the left auricle had a normal contour, without any systolic pulsation during ventricular systole. The antero-posterior view is shown in the illustration; the right side seems to be a little enlarged (Fig. 1). The cardiogram shows slight right axis deviation (Fig. 2).

Discussion

It is certain that the murmur was not there before the accident. It seems to have developed as a result of the blow on the chest; not at once, but after a latent period, perhaps about a fortnight. No symptoms accompanied the appearance of whatever lesion it is due to. Such a thrill and murmur may suddenly appear in the heart from three possible causes, and they may all arise from indirect violence.

Rupture of a chorda tendinea of the mitral valve usually results from disease. Bailey and Hickham (1944) describe cases in which there was the sudden appearance of a mitral systolic murmur and thrill between the apex and the left border of the sternum, conducted to the axilla. The left auricle becomes enlarged and may pulsate. Failure may develop,

with fibrillation, soon or only after years. Frothingham and Hass (1934) have described the rupture of a normal chorda from indirect violence.

Rupture of a papillary muscle of the mitral valve is usually a very grave occurrence. The same signs are produced. In the case of Glendy and White (1936) trauma was the cause. It may occur after infarction (Morargues, 1939). In Anderson's case (1940) there were a systolic murmur and thrill conducted to the axilla; at first there was failure but later a good recovery. The site of the murmur suggests that it was due to the rupture of a valve, but one cannot entirely exclude the septum. For the most part rupture of a papillary muscle of the mitral valve is more serious than rupture of a chorda tendinea, and leads to the onset of rapid fatal failure. Perforation of the interventricular septum is met with from time to time after myocardial infarction. I have seen it arise from an abscess. There may be symptoms of pain, shock, and dyspnœa (Stanley, 1937), with the rapid appearance of failure of the right ventricle. On the other hand there may be no symptoms at all, and but little ill-effect (Wood, 1944). A mid-præcordial thrill and murmur at systole are usually described, such as are produced by the congenital lesion. The acquired perforation is usually low down in the septum (Gross and Schwartz, 1936). Damage to the myocardium may cause angina pectoris (Campbell, 1939). The contused area may become the site of an aneurysm (O'Farrell, 1939) and perhaps rupture later. Indirect violence to the heart may damage the septum itself; for partial heart block has been recorded from the effects of blast (Campbell, 1943), and from a crushing injury (Barber, 1942); complete block has also been noted (Coffer *et al.* 1941).

The signs in this case suggest that rupture of the interventricular septum occurred. The site of the thrill and murmur and the absence of any effect on the left auricle or on the efficiency of the heart are in favour of this diagnosis. One might suggest that the septum softened, and ruptured some time after the accident, perhaps giving way gradually, so that no sudden disturbance occurred. If the membranous portion had given way, this would probably have happened at once. In any case it is most unlikely to do so unless it is the site of a congenital aneurysm.

The original description of Henri Roger (1879) is worth recalling, for he made his diagnosis some years before an autopsy confirmed it. He described "a murmur loud and long; it is single, begins at systole, and is prolonged so as to hide the natural tic-tac; it has its maximum, neither at the apex, nor at the right base, nor at the left, but in the upper third of the præcordial region; it is median, like the septum itself; and from this central point it diminishes evenly in intensity and by degrees, accordingly as one gets further away from it; it is local and without propagation into the vessels. It coincides with no sign of organic disease other than the thrill. An abnormal murmur which comprises this combination of character is the pathognomonic sign of patency of the septum of the ventricles." The remark of one of those who heard this communication of course applies to the case described here. "C'est là une circonstance regrettable, il faudrait au moins une observation avec autopsie."

Conclusion

With this precedent of Roger, the proposed diagnosis is traumatic rupture of the interventricular septum. The history and physical signs in such a case are described.

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MULTIPLE CHEST LEAD CARDIOGRAMS AND THEIR CLINICAL VALUE*

BY

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The following is a brief contribution to the study of multiple chest lead cardiograms and an assessment of their diagnostic value in a series of 302 cases.

The cardiogram obtained by placing an electrode on the surface of the heart and pairing it with an electrode placed upon a distant part of the body was studied in experimental animals by Lewis and Rothschild in 1915. This pioneer work laid the foundation of modern chest lead cardiograms. The essential parts of Lewis and Rothschild's work were confirmed by numerous animal experiments and by a unique clinical test performed on an exposed human heart by Barker, McLeod, Alexander, and Wilson in 1929. Subsequent investigations have been made by Wolferth and Wood, 1932; Wilson, Hill, and Johnston, 1934; Johnston, Hill, and Wilson, 1935; Kossmann and Johnston, 1935; Wilson, Johnston, and Hill, 1935; Wood and Selzer, 1939; Evans, 1939; and Wilson *et al.*, 1944; these have gone far to elucidate the præcordial cardiogram in normal and abnormal hearts and to show that the tracings obtained from the præcordium are essentially the same as those obtained direct from the underlying pericardial surface.

In putting together the following notes, wherein an attempt is made to explain the initial deflections of the præcordial electrocardiogram, the experimental work of these investigators has been freely drawn upon. The form of any cardiogram depends primarily upon the fact that, although the muscle fibres in the heart follow an oblique or circuitous course, the frequent branching and inter-communication between them enables the wave of excitation to pass fairly directly from the endocardial to the pericardial surface. In fact, having quickly traversed the Purkinje system, the excitatory process appears to spread almost centrifugally outwards from the ventricular cavities. We may, therefore, visualize during the QRS interval a wave of positive potential followed closely by a wave of negative potential spreading outwards from each ventricular cavity. These positive and negative charges are held apart by an electromotive force similar to that between the poles of a battery. The contracting muscle over which the wave has passed and the quiescent muscle ahead of the wave behave as normal electrical conductors. Thus the negative potential generated at the proximal side of the wave is conducted backwards to the ventricular cavities and the positive potential generated at the distal side of the wave is conducted outwards to the pericardial surface of the ventricles, but they are not able to neutralize each other by passing in the reverse direction across the wave of excitation. On the contrary, the difference of potential appears to increase as the wave travels so that, within limits, the thicker the ventricular wall, the greater will be the potential difference between its endocardial and pericardial surfaces. Also, where the heart is nearest to the chest wall, its potential will reach an overlying præcordial electrode with the smallest amount of loss in transmission.

From the foregoing principles it follows that the ventricular cavity remains negative so long as the wave of excitation is spreading through any part of the heart muscle, i.e. throughout the QRS interval, after which it returns quickly to zero potential. It is also clear that the pericardial surface is positive for at least part, and nearly always the first part, of the QRS interval. At any point on the pericardial surface, however, the potential switches suddenly to that of the ventricular cavity as soon as that point is reached by the wave of excitation, the

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underlying muscle then behaving as a normal electrical conductor. The negative potential of the ventricular cavities is conducted backwards, upwards, and to the right through the auricles and great vessels and is transmitted chiefly to the right upper quadrant of the body which consequently remains negative throughout the QRS interval. Some of the negative charge is, however, conducted forwards from the right auricle and tends to neutralize the positive potential of the adjacent right ventricular pericardium. The positive potential of the pericardial surface of the ventricular muscle on the other hand is chiefly conducted forwards and downwards and to the left, and so dominates the electrical field in the front, left lower, and (usually to a lesser extent) the left upper quadrants of the body.

The initial ventricular deflections of the normal præcordial cardiogram consist of an upstroke (ascending limb of R) followed by a deep rapid downstroke (intrinsic deflection of Lewis, descending limb of R and S) and then a return to the iso-electric line. The upstroke is made by the rise of positive potential at the pericardial surface underlying the electrode as the wave of excitation approaches. The intrinsic deflection is made by the rapid switching of the potential at the pericardial surface to that of the ventricular cavity and signalizes the arrival of the wave of excitation at the point on the pericardial surface underlying the electrode, and the return to the iso-electric line is made by the disappearance of the negative potential of the ventricular cavities which may be rapid or relatively gradual according to whether the excitatory process is still spreading through other parts of the heart. Generally speaking, as the examining electrode is moved from right to left across the præcordium it draws closer to the heart muscle which at the same time becomes thicker. When it has passed the septum it begins to move further away from the bifurcation of the bundle and when it has passed the apex it begins to move further away from the surface of the heart. Hence, with a certain reservation that will be mentioned later, the R wave in the cardiogram becomes progressively higher as the electrode moves from the right border to the apex, after which it becomes lower, and it occurs progressively later as the electrode moves from the septum to the axilla.

Frequently the onset of the excitatory process in the septum and adjacent parts of the ventricular wall causes the ventricular cavity to become slightly negative before the impulse has finished spreading through the most distant parts of the Purkinje network. In this event, when a tracing is taken from the left side of the præcordium the negative potential is conducted electrically from the cavity through the as yet quiescent muscle underlying the electrode and causes a negative deflection (descending limb of the Q wave) in the cardiogram. The R wave then occurs relatively late in the QRS interval and the arrival of the wave of excitation at the pericardial surface underlying the electrode will mark the end or very nearly the end of the excitatory process in the heart. It will therefore mark the end or very nearly the end of the negative potential in the ventricular cavities. Thus the intrinsic deflection in the cardiogram will terminate at or very near the base line and there will be little or no S wave. The behaviour of the T wave is still in some cases obscure. Although it is well known that during the T wave the myocardium is relaxing, the nature of this process and its variations from normal are not so clearly understood. Its interpretation, therefore, remains to some extent empirical.

Characteristic variations from the normal QRS complexes are produced by certain forms of ventricular hypertrophy or damage. In the case of left ventricular preponderance the normal differences between the two sides of the præcordium are increased. On the right side of the præcordium the positive potential is apparently neutralized by the increased negative potential generated in the left ventricle and conducted from the cavity of that ventricle through the auricles and adjacent tissues. Consequently the R wave is very small or absent and the S wave is deeper and somewhat wider than usual. Complexes of this type extend well across the præcordium and may be obtained from the apex. Still further to the left the R wave suddenly becomes abnormally high and rather wide and tends to occur rather late, and is therefore frequently preceded by a Q wave. The transition from the small to the high R wave observed in the 3rd, 4th, or 5th chest lead is marked by inversion of the T wave.

In right ventricular preponderance the R wave is highest on the right side of the præcordium usually in the 2nd or 3rd chest lead, where T is frequently inverted and Q may be present, S is small or absent. In this condition leads from the left side show a small R similar to that normally found on the right side and S is correspondingly deep; T is upright.

In bundle branch block the septum on the affected side distal to the block remains quiescent until the excitatory process from the unaffected side has spread through the septum. While the septum is the seat of a spreading excitatory process, positive potential is generated upon its quiescent surface. This is conducted through the cavity and free wall of the ventricle and results in a small R wave on the affected side of the præcordium. The completion of the excitatory process in the septum causes the potential of the affected side to switch to that of the opposite ventricular cavity. This negative potential causes an S wave or a notch upon the R wave in tracings from the præcordium on the affected side. The subsequent spread of the excitatory process in the free wall of the affected ventricle causes a second rise of positive potential which reaches the chest wall far out on the affected side. There will thus be a secondary R wave which may be followed by a more or less normal intrinsic deflection or the return to the base line may be rather slurred. In the case of left bundle branch block the secondary R wave is frequently obtained only from the axillary leads. Tracings from the præcordium overlying the normal bundle differ from the normal cardiogram only in that the R wave is small or absent and the return of the S wave to the iso-electric line is delayed. The widening of S is due to the late excitatory process in the opposite ventricle, the negative potential generated therein being conducted across the septum and through the cavity and contracting free wall of the normal ventricle, and so to the præcordium.

In myocardial infarction the damaged muscle conducts electricity in a normal manner, but cannot respond to the wave of excitation. If the infarct involves the whole thickness of the ventricular wall, the potential of its pericardial surface must at all times be that of the ventricular cavity. It is therefore negative throughout the QRS interval and there is no R wave in the cardiogram from that region. The T wave is inverted over the infarct and over a region surrounding the infarct where the myocardial changes are of minor degree. If the infarct involves the endocardial surface, but not the whole thickness of the ventricular wall, the negative potential of the ventricular cavity is at first conducted through infarct and normal muscle to the surface of the chest, and the first part of the QRS complex consists of a Q wave. Then, as the wave of excitation, spreading outwards around the periphery of the infarct, reaches and spreads through the normal muscle between the infarct and the pericardial surface an upstroke will be registered which may or may not go above the base line. On the arrival of the excitatory process at the pericardial surface overlying the infarct there is a return to zero potential unless the excitatory process is still spreading through other parts of the heart, in which case there will be a secondary negative wave.

From these considerations it will be apparent that the QRS complexes of the præcordial cardiograms, unlike those of the standard leads whose interpretation is still largely empirical, lend themselves to rational interpretation and that most of the common findings can be explained in terms of myocardial pathology.

Results Obtained

Before proceeding to analyse a series of cardiograms, certain points of technique call for consideration. If, as in the series under review, the præcordial electrode is paired with the left lower limb, the tracing will be modified by the potential variations of the limb, and as this is almost always positive during the QRS interval and during the T wave, the result will be a shift towards negative voltage in the cardiogram; and a fictitious absence of the R wave or inversion of the T wave will sometimes occur. The error from this source is equal to one third of the algebraic sum of standard leads II and III. The necessary correction would be relatively simple if it applied to the summits of the waves. Unfortunately it applies only to the height of the wave at a given moment of time and as the summits of the three leads concerned are not in phase and usually do not coincide, the correction is too complicated for routine practice. In all cases in the present series where an abnormality was present or suspected, the above correction was, however, applied before interpretation of the findings. A better method is to pair the præcordial electrode with a neutral area (Wolferth and Livezey, 1944), or, as we now prefer, a central terminal such as Goldberger's modification of the Wilson assembly (Goldberger, 1942).

Brief mention must also be made of the points chosen for the præcordial electrode. In

their supplementary report (1938) the committee of the American Heart Association recommended a number of standard positions related to the surface markings of the chest wall irrespective of the size and position of the heart. Thus the committee recommended that the fourth position be at the intersection of the left mid-clavicular line and the fifth space, and that the third position be midway between this point and the left border of the sternum in the fourth space. As, however, the aim of this investigation was to study the electrical field overlying particular areas of the heart's surface, it was thought desirable that the points selected on the chest wall should bear as constant a relationship as possible to the anatomy of the heart. It has, therefore, been the practice in all the cardiograms now under review to take the fourth chest lead from the outer border of the cardiac apex instead of from the mid-clavicular line whose relation to the heart is variable, and to take the third chest lead from a point midway between the apex and the left sternal border in the fourth space. In cases where the impulse cannot be clearly felt the apex is assumed to be in the mid-clavicular line.

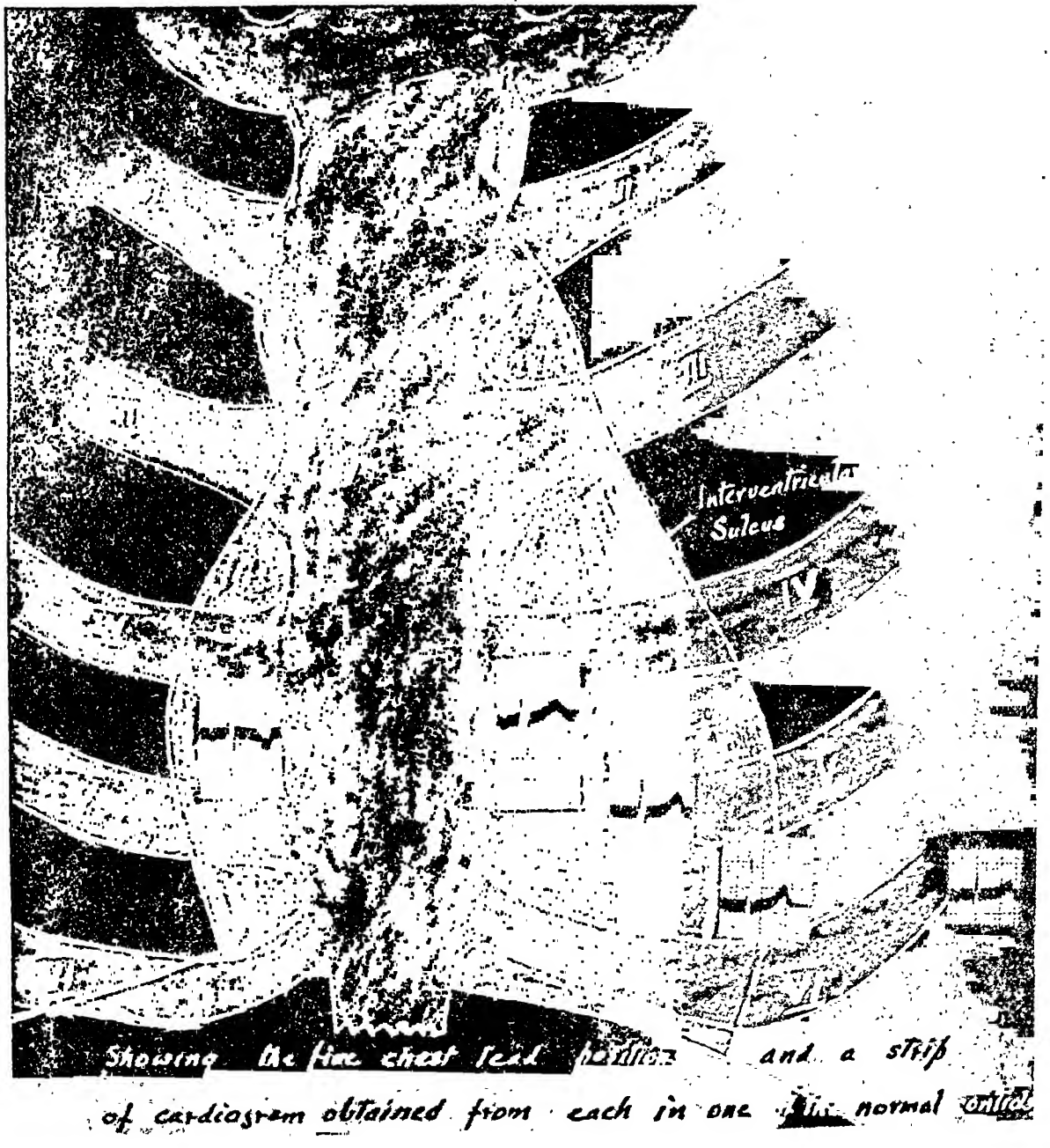

FIG. 1.

This method has also the advantage that the fourth chest lead is identical with lead IV, provided it has been paired with the same indifferent electrode. This is of some importance when a comparison is being made with other cardiograms where only one præcordial lead has been taken. In all other respects the recommendations of the committee of the American Heart Association have been followed. The five points are indicated in the figure by portions of the cardiogram obtained therefrom in a normal subject.

The following is a study of 302 cases in which five chest lead cardiograms CF 1, 2, 3, 4, and 5 were taken and in which full clinical histories were available. They include 218 cases from private practice, being all the cases in which a cardiogram was considered necessary between certain dates, 78 hospital cases, and 6 normal controls. The hospital group comprises all the cases in which a cardiogram was taken during a limited period when all cardiograms were taken with multiple chest leads. With the exception of the 6 controls they all had real or suspected heart disease, but otherwise they were in no way selected. In a short series the average time required for the taking of the five chest leads after the completion of the standard leads was four minutes. All the cardiograms were re-examined and classified under nine headings according to the diagnostic information gleaned from the standard leads on the one hand and the chest leads on the other. In making the classification the standard lead cardiogram was considered doubtful when the QRS complexes were of low voltage (total deflections of the three leads less than 15 mm.), or when the R S–T take off was depressed 1 mm. in leads I or II, or the T wave in these leads measured only 0·5 mm. Ventricular preponderance was considered abnormal, but axis deviation without T wave inversion or significant R S–T displacement was ignored. The chest lead cardiogram was considered doubtful when the maximum T wave was between 1 and 2 mm. or where splintering without widening occurred in one of the S waves from the right side of the heart or where there was a dip of 1 mm. in the R or T gradients.

TABLE I

A Comparison of the Frequency with which Abnormalities were revealed by Standard and Chest Leads in a Series of 302 Cases

Standard Leads	Normal	Normal	Normal	Doubtful	Doubtful	Doubtful	Abnormal	Abnormal	Abnormal
Chest leads	Normal	Abnormal	Doubtful	Abnormal	Doubtful	Normal	Normal	Doubtful	Abnormal
Number of cases	122	40	19	29	8	6	3	2	65
Percentage of cases	*41*	*13·5*	*6·5*	*10*	*3*	*2*	*1*	*1*	*22*

Table I shows that the standard leads were normal in 181 cases and of these the chest leads were abnormal in 40 and doubtful in 19; the standard leads were doubtful in 43 cases and of these the chest leads were abnormal in 29, doubtful in 9 and normal in 6; the standard leads were abnormal in 70 cases and of these the chest leads were normal in only 3 and doubtful in 2. Both were normal in 122 cases and abnormal in 65 cases; of these 65 cases the chest leads were considered to yield extra information in 27. These were cases in which an arrhythmia or prolonged P–R interval or ventricular preponderance was the only abnormality present in the standard leads and where the chest leads revealed QRS splintering or a major fault in the R or T wave gradient, amounting in many cases to evidence of infarction. An analysis of the clinical histories of the 69 cases in which the cardiogram was normal in the standard leads and abnormal or doubtful in the chest leads may be set out as follows.

Certain cardiac pathology

Strong history of myocardial infarction with or without angina of effort	32
Congestive heart failure	3
Hypertension with left ventricular hypertrophy	1
Congenital pulmonary stenosis with septal defect	1
Previous history of failure with complete heart block lasting 5 days	1
Asthma with right ventricular hypertrophy	1
Total with definite cardiac pathology	39 (56 per cent)

Probable cardiac pathology

Angina of effort with no clear history of infarction	8
Recent severe rheumatic fever	1
Sternal or præcordial pain probably due to coronary spasm	8
Increasing effort dyspnoea or palpitation	7
Thyrotoxicosis	1
Paroxysmal tachycardia, poor effort tolerance with tic-tac rhythm	1
Congenital aneurysm of descending aorta pressing upon the heart (ruptured three weeks later)	1
TOTAL with probable cardiac pathology	27 (39 per cent)

Possible cardiac pathology

Sternal or præcordial pain probably not cardiac	3
Asthma (heart not screened)	1
TOTAL with possible cardiac pathology	3 (4 per cent)

There were only five cases in which the cardiogram was normal or doubtful in the chest leads and abnormal in the standard leads. The following is an analysis of these.

Certain cardiac pathology

Strong history of myocardial infarction with angina of effort	3
Aortic incompetence and slight right and left ventricular hypertrophy	1
TOTAL	4

Probable cardiac pathology

P–R interval 0·21 sec. (normal P–R interval chest leads)	1

All the cases of myocardial infarction were of the T III (posterior) type.

The above figures show conclusively that where the standard leads are normal or doubtful and the chest leads are abnormal, the clinical findings (except in cases of posterior infarction) strongly support the chest leads. It was noted that the lead from the apex indicated myocardial damage rather more frequently than any other single lead. At the same time, out of 40 cases in which the chest leads provided the sole cardiographic evidence of disease, that evidence was solely present in leads other than the apical in 21. In all but two of these the diagnosis of myocardial damage was supported by strong or fairly strong clinical evidence.

Measurements of the amplitudes of the R and T waves of all the chest leads were made in 192 consecutive cases and in 40 other selected cases. The selected group comprised all the remaining cases with abnormal chest leads (34) and 6 normal controls, three of the latter being tall and slender and three short and broad. If the amplitudes of the R waves in the five chest leads are plotted graphically in order from the 1st to the 5th chest lead, a curve is obtained that represents the distribution of positive potential across the præcordium during the spread of the excitatory process through the heart: for convenience we shall call it the R gradient. Similarly, if the amplitudes of the T waves are plotted in the same order, a curve will be obtained which may be termed the T gradient. Kossman and Johnston (1935), from a study of 30 normal students, observed that " the average voltage of the R deflection increased progressively in the first four præcordial leads and was nearly as great in the fifth as in the fourth." They also noted that " the average voltage of the T wave was greatest in the 2nd and 3rd præcordial leads and showed a progressive decrease in leads taken further to the left." These observations prompted the following study of the R and T gradients.

In slightly more than half (58 per cent of our series) the form of the R gradient supported Kossman and Johnston's findings. But in a considerable number some portion of the gradient was flat or even presented a dip. An analysis showed that the gradient was flat from the second to the third lead in 23 cases (10 per cent of the series), from the first to the second lead in 16 cases (17 per cent), from the first to the third in 6 cases (3 per cent), from the first to the fourth in 7 cases (3 per cent), and from the second to the fourth in 6 cases (3 per cent). In all cases in which the gradient was flat from the first to the fourth leads the amplitude of the R wave was zero, and of the 6 in which the gradient was flat from the second to the fourth chest leads the amplitude was zero in 3 and 1 mm. in 3 cases. In both these groups there was clinical or cardiographic evidence of myocardial damage (apart from the R waves) in all the cases. In 27 cases (12 per cent), a rising or horizontal R gradient was observed to dip slightly and to rise again as the electrode moved further to the left. In 17 cases (7 per cent)

a similar dip was observed in the T gradient and in 6 of these a dip occurred in both gradients together. It should be emphasized that a dip in the T gradient does not necessarily imply inversion. All the cases presenting a plateau or a dip in the gradient were classified under four heads according to whether on clinical or other evidence it was considered that myocardial damage was certain, probable, possible, or absent.

The results are set out in Table II showing the number of cases in each group and the percentage of the various grades of myocardial damage in each group and for the whole series. It will be observed that myocardial disease was present in 46 per cent, and probably in another 14 per cent, these two groups together comprising 60 per cent of the whole series. In the group with a flat gradient from 1 to 2 there were 63 per cent with definite pathology, and 6 per cent with probable pathology, making a total of 69 per cent with definite or probable pathology. In the group with a flat gradient from 2 to 3 the figures were 57 per cent and 17 per cent, making a total of 74 per cent with definite or probable myocardial pathology. In the group with a flat gradient from 1 to 3 the figures were 67 per cent and 16 per cent, making a a total of 83 per cent. In the groups with a flat gradient from the 1st to the 4th, or from the 2nd to the 4th, there was, as previously stated, clear myocardial pathology in all cases.

TABLE II

THE ASSOCIATION BETWEEN MYOCARDIAL DAMAGE AND SOME FEATURES OF THE R AND T GRADIENTS

Leads involved	Flat portion of R gradient					Dip in R gradient		Dip in T gradient		Dip common to both gradients	Whole Series
	1 & 2	2 & 3	1, 2, 3	1, 2, 3, 4	2, 3, 4	Greater than 1 mm.	1 mm. or less	Greater than 1 mm.	1 mm. or less		
No. of cases	16	23	6	7	6	10	17	12	5	6	232
Myocardial Pathology: Certain	10	13	4	7	6	6	10	8	1	3	106
	63%	*57%*	*67%*	*100%*	*100%*	*60%*	*59%*	*67%*	*20%*	*50%*	*46%*
Probable	1	4	1	—	—	1	3	2	—	—	33
	6%	*17%*	*16%*	—	—	*10%*	*18%*	*17%*	—	—	*14%*
Certain and probable combined	*69%*	*74%*	*83%*	*100%*	*100%*	*70%*	*76%*	*83%*	*20%*	*50%*	*60%*
Possible	3	5	1	—	—	3	3	2	1	2	55
Absent	2	1	—	—	—	—	1	—	3	1	38

There would thus appear to be a real correlation between a plateau upon the R gradient and the presence of myocardial damage specially when the plateau involves the 2nd, 3rd, and 4th chest leads. It was noted, however, that such a plateau was in many cases associated with low R wave voltages which are in themselves of some diagnostic import.

It will also be seen from Table II that the incidence of certain myocardial pathology is somewhat higher than the average for the series in those cases showing a dip in the R gradient, whether greater or less than 1 mm. and in those cases showing a dip of more than 1 mm. in the T gradient. The incidence of probable myocardial pathology in these groups as a whole, however, is not significantly above the average for the whole series. It is also apparent that in cases where the dip in the T wave is 1 mm. or less, or where a dip occurs in both gradients simultaneously, the incidence of certain and probable myocardial pathology taken together is below the average. Furthermore, one of the 6 normal cases presented a small dip in both R and T gradients. It was observed that a majority of the dips in the gradients occurred in the third chest lead, which in this series of cases was taken, as previously mentioned, from the region overlying the septum and interventricular sulcus. In this sulcus lies the coronary artery embedded sometimes in a considerable thickness of fat, which, as Kaufman and Johnston, 1943, have pointed out, is a very poor electrical conductor. Thus, not only does the heart muscle in this situation dip slightly away from the chest wall, but there is also interposed the high resistance of a layer of fat. It would seem that this would be sufficient to

account for a dip in both R and T gradients. It would not, however, explain a dip occurring in the second or fourth lead.

In Table III, therefore, the gradients are grouped according to whether the dip occurs in the third lead alone, or whether the second or fourth chest lead is involved either alone or in addition to the third, and the correlation of the two groups with the presence of myocardial damage is shown. It will be seen that when the third lead alone is involved, the incidence of certain and probable myocardial damage is only slightly higher than the average for the whole series. When the second lead is involved, the incidence of certain myocardial damage is 75 per cent, and when the fourth lead is involved, the incidence of certain myocardial damage is 100 per cent in the case of the R gradient and 86 per cent in the case of the T gradient. In the remaining case showing a dip in the T gradient in the fourth lead myocardial damage was considered clinically probable. It was also observed that when there was an R wave, however small, in the first lead and no R or R^1 in the second lead, myocardial pathology was present in every case. It would appear, therefore, that while a dip in either or both gradients in the third lead alone is of little or no significance, a dip of any degree involving the second or fourth lead is strongly indicative of myocardial damage. In clinical practice all the features of the R and T gradients can readily be appreciated by the eye without any graphical plotting and actual measurements are seldom required.

TABLE III

THE ASSOCIATION BETWEEN MYOCARDIAL DAMAGE AND THE POSITION OF THE DIP IN THE R AND T GRADIENTS

Myocardial Pathology	Dip in R gradient			Dip in T Gradient		Whole series
	In 3rd lead only	Involving 2nd lead	Involving 4th lead	In 3rd lead only	Involving 4th lead	
Certain	10 (47%)	3 (75%)	6 (100%)	3 (30%)	6 (86%)	(46%)
Probable	4 (19%)	—	—	1 (10%)	1 (14%)	(14%)
Possible	6 (29%)	1 (25%)	—	3 (30%)	—	(24%)
Absent	1 (5%)	—	—	3 (30%)	—	(16%)

One further comment should be made on the third chest lead. Two cases of marked QRS splintering in this lead were associated with very doubtful clinical histories of myocardial damage. As the examining electrode in this lead is astride both ventricles it is conceivable that some anatomical asymmetry in the arrangement of the conducting mechanism on the two sides may account for such splintering in rare cases. It may not, therefore, necessarily indicate any pathology and pending further investigation it is suggested that this finding be interpreted with caution.

CONCLUSIONS

The principles underlying the interpretation of chest leads are discussed.

The normal R and T gradients obtained from multiple chest leads are described.

An analysis is made of a series of 302 cases in which multiple chest leads CF 1, 2, 3, 4, and 5 were taken, and from this the observations that follow were made.

The chest leads provided the sole electrocardiographic evidence of myocardial damage in 40 cases (13 per cent) and of these the evidence was solely present in leads other than the apical in 21.

When the fourth lead was involved in a plateau or a dip of the R gradient, myocardial damage was present in every case; and when the second lead was involved in a dip of the R gradient or the fourth lead in a dip of the T gradient damage was present in a high proportion of cases.

A dip of the R or T or both gradients in the third lead is a normal finding.

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HEART BLOCK IN A DIABETIC WITH ONLY MILD ARTERIOSCLEROSIS

BY

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Adams-Stokes attacks were observed in an elderly diabetic in whom clinical and anatomical manifestations of arteriosclerosis were minimal. A relation, however, between the underlying cardiac disturbance and the metabolic changes of diabetes was evident. Some rather unusual electrocardiograms were obtained during Adams-Stokes attacks. In view of these uncommon features, and since we have failed to find reports of similar cases, it seemed worth while reporting it in detail.

A dental surgeon, 58 years old, was admitted to hospital with mild collapse and heart failure on December 24, 1942. His mother suffered from hypertension and one brother from diabetes.

He was born in Palestine, and had had malaria in his youth. He had never been seriously ill until 1929, when he became diabetic. Thereafter he was under the regular care of his physician, Dr. Korkidi, to whom we wish to express our gratitude for his kind co-operation and for the material provided by him. His diabetes proved to be rather severe, but was fairly well controlled by almost regular insulin injections during the course of many years. Except for a few pyodermic complications (a furuncle of the lip and a phlegmone of the hand in 1936) he had never been obliged to stop work in his dental practice. His blood sugar fluctuated between 167–386 mg. per 100 c.c.; his urine was mostly sugar-free and contained only occasionally 0.1–1 per cent of sugar. Traces of acetone were detected only very rarely. His weight was always normal.

In 1935 he complained of exceptional weakness; his physician noted a slight muffling of the first mitral sound and a blood pressure of 95/70, whereas his blood pressure had always been normal before and remained so afterwards. Later on, no cardiovascular irregularities were observed; examinations of the blood for urea, Wassermann reaction, etc. gave normal results. His pulse rate was usually about 60. He had never had any anginal pain and hypertension was never noted.

In the middle of 1941, when trying a patent medicine for his diabetes on his own initiative (extract of an Indian mushroom (?) according to his description), and discontinuing his usual dose of insulin, he fainted after a few days and had an attack of convulsions accompanied by unconsciousness. After he had regained consciousness, insulin and stimulants were administered. After a few more attacks he was admitted to the Neurological Department of the hospital (Dr. L. Halpern) in May 1942. A thorough examination, including analyses of the spinal fluid, did not reveal any abnormal findings. The Wassermann reaction in blood and cerebrospinal fluid was negative. His blood sugar at that time was 200 mg. per 100 c.c. sugar. A presumptive diagnosis of idiopathic epilepsy was made and treatment was started with impronal (a barbiturate), epanutin, calcium, and parathyroid. Under this treatment a few more attacks occurred.

During the few weeks prior to his admission to the Medical Division, insulin was decreased from 40 to 30 units a day because of a continuous fall in blood sugar. The evening injection on December 23 was given from an ampoule which contained 60 units per c.c. instead of the usual 20 units; as this difference in content was accidentally overlooked the patient got 45 instead of 15 units. Some time later, when feeling that he was " suffering from insulin shock," he took some sweets and glucose. Shortly afterwards a continuous series of convulsive seizures set in accompanied by complete loss of consciousness and of control of the sphincters. During these attacks a very slow pulse was observed by his house physician. Atropine, camphor, glucose intravenously, and ephedrine were subsequently administered but proved to be of little avail. On the following morning when the attacks finally stopped, his blood sugar was 597 mg. per 100 c.c.

On admission the patient was pale, his extremities were cold, his consciousness was normal, his response somewhat sluggish. He did not complain of any pain or dyspnœa. His pupils reacted to light. The lungs were normal. His heart was in normal limits, the sounds somewhat dull, the pulse urea rate 26–28 a minute, the blood pressure 135/45. The liver was slightly enlarged and tender. Blood urea was 67 mg., later 28–42 mg., cholesterol 272–151 mg., each per 100 c.c. X-ray examination of the heart showed slight diffuse enlargement. Urine analysis revealed only traces of albumin in an occasional specimen. A diagnosis of heart block accompanied by Adams-Stokes seizures was made. Fig. 1 confirmed complete heart block auricular rate 86, ventricular rate 17. The blood

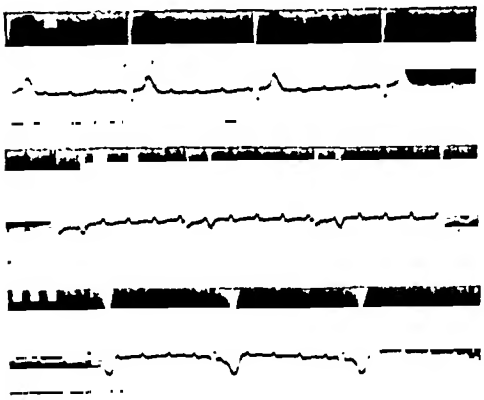

FIG. 1.

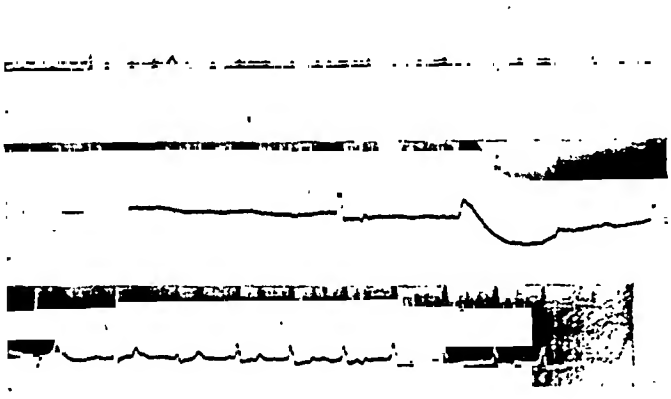

FIG. 2.

sugar was 430 mg. per 100 c.c. at noon. Altogether 40 units of insulin were given. In the afternoon a new series of attacks began: during one and a quarter hours the patient intermittently fell into unconsciousness preceded by a slowing down of the heart action—the critical rate apparently being 22—until the pulse and heart sounds finally disappeared. One cardiac standstill lasted 55 seconds. It is traced in Fig. 2 showing gradual stoppage of ventricular action, and afterwards of auricular action, reaching a complete standstill both mechanically and graphically. After the zero line the film shows one irregular deflection caused by a violent convulsion. Ventricular action sets in, as a result of different pacemakers (Fig. 3), finally at a rather constant rate of 50, whereas for a certain time no sinus pacemaker and no rhythmic action of the auricles can be made out (Fig. 4).

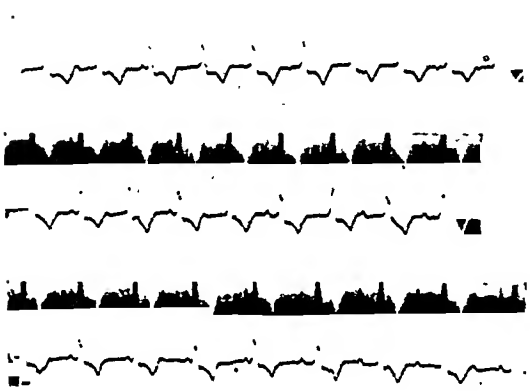

FIG. 3.

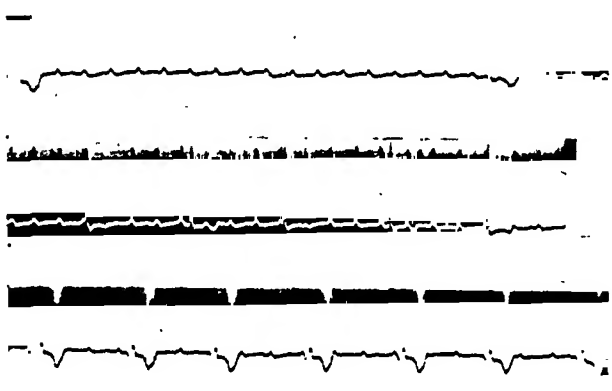

FIG. 4.

Another but shorter attack is recorded showing rhythmic P waves, 92 a minute, and subsequently it changes again to complete block (lead II). Respiration usually faded away a short while before the pulse stopped and breathing recurred increasing in its amplitude before the action of the heart could be noticed again. Thus a perfect Cheyne-Stokes periodicity could be observed, somewhat overlapping the Adams-Stokes periodicity of the heart. Several attacks recurred the following night. After 40 units of insulin the morning blood sugar was 136 mg. per 100 c.c. On the following day no attacks occurred. On December 26 blood sugar in the morning was 370 mg. per 100 c.c.; at noon a series of attacks occurred. It was noted that every time the pulse returned it was quicker, about 36, and sometimes even nearly 50 for a few seconds; furthermore the blood pressure was 150/60 instead of 140/50 before the Adams-Stokes attack. When, subsequently, the diabetes was kept under control,

no further attacks occurred for over a month, although the pulse remained slow. Complete block had become re-established.

Up to January 13, 1943, nothing in particular was noted except a continuous improvement of diabetic tolerance. Insulin was correspondingly decreased to 5–10 units in the morning. On January 13, the patient began to run a temperature of 37·8–38·8 for three days, due to a small pulmonary infiltration. His pulse rate during the course of this complication was 32–38. His diabetic balance was not affected at all and finally insulin was no longer considered necessary (aglycosuria, blood sugar 176 mg. per 100 c.c. on January 28). The patient's diet contained 150 g. carbohydrate, 70 g. fat, 60 g. protein. On February 3, a whole sequence of severe convulsive seizures started without any apparent reason except, possibly, a slight irregularity in his regime. The following morning, the blood sugar rose to 500 mg. per 100 c.c., and the patient entered into diabetic coma. 90 units of insulin had to be given, partly intravenously, and the blood sugar was decreased to 310 mg. per 100 c.c. A series of severe attacks led to a state of complete asphyxia and cardiac standstill, lasting about three minutes, and death seemed imminent or had apparently already occurred. An intracardiac injection of caffeine and procardin (coramin) was resorted to and the injecting needle, previously motionless, began to show cardiac contractions, in the beginning at a rate of 60, afterwards decreasing to his usual bradycardia. A short while later, after an injection of insulin, the patient partly recovered consciousness, passing gradually through a state of paraphasia and disorientation to a normal mental condition. As usual, he was completely amnestic as to the entire course of events. On February 8 he had a mild attack, probably as a consequence of an insulin reaction, which was stopped by glucose—an event which occurred several times during this period. A quantity of 25–40 units of insulin applied in three separate injections was necessary to keep the diabetes under a certain, even if unsatisfactory, control—the blood sugar being between 250–300 mg. per 100 c.c., glycosuria between 15–50 g. per day, and sometimes even reaching 80 g. Periods of a few days without attacks alternated with a day or two when attacks occurred. The relation between diabetes and cardiac disturbance became more and more blurred, but it must be stressed, as already pointed out, that satisfactory control of the diabetes was no longer obtained. He was transferred to protamin zinc insulin, 20–30 units. For about a fortnight seizures occurred but rarely; regular insulin 10–15 units had to be added. On March 10 a series of violent attacks began, one rapidly following the other and the patient died on March 13, 1943, without recovering consciousness. Fig. 5, taken during an attack, shows transient ventricular standstill interrupted by isolated ventricular impulses, afterwards ventricular trachycardia followed by decreasing auricular action with complete ventricular

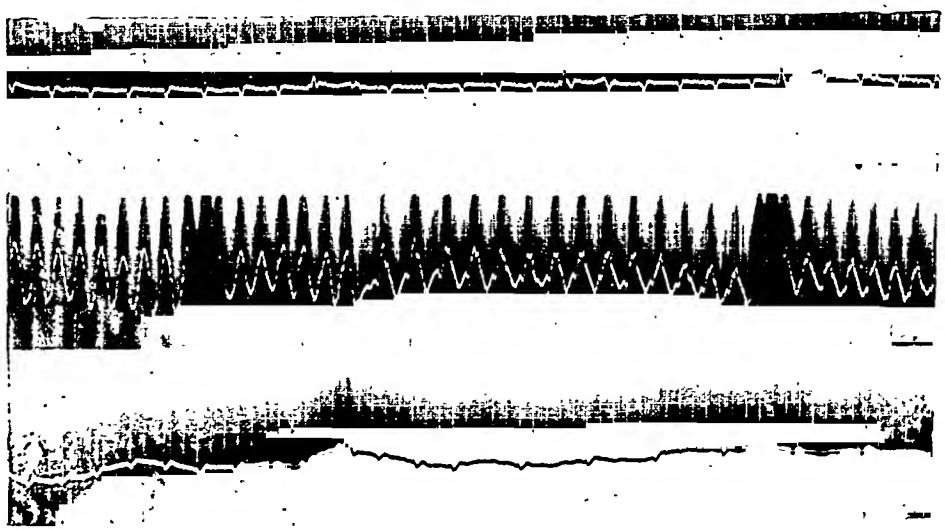

FIG. 5.

standstill. The particular frequency and violence of these attacks may partly be attributed to their occurring during a severe " khamsin " (a hot and dry wind, common in the Eastern Mediterranean), the occurrence of which is often connected with cardiovascular disturbances.

Autopsy (performed by Dr. B. Gellei).

Nervous system: No particular findings.

Cardiovascular system: Heart: slightly enlarged (weight 385 g.) with mild left hypertrophy and dilatation. No gross lesions of the myocardium. Generalized arteriosclerosis of a middle degree

of the aorta with calcified plaques (near to the arteriae iliacae), and of its main branches; mild arteriosclerosis of the coronary arteries.

Lungs: Bronchopneumonic infiltration in the left lower lobe.

Liver and pancreas: No gross findings.

Kidneys: Of normal size, somewhat firm: surface smooth except for scattered areas which are slightly granular.

Microscopic examination.

Heart: Specimens taken from the right and left ventricles, from the A-V node, the A-V bundle and the origin of its two branches, as well as from the lower part of the interventricular septum, showed no pathological changes. Serial sections taken from the A-V system showed no pathological findings. In the right lower portion of the fibrous septum there were several foci of calcification without connection with the right bundle branch. The myocardium is normal. The arteries show very mild arteriosclerosis. Glycogen stain taken from a section of the anterior wall of the left ventricle: glycogen positive, small droplets of glucogen, larger droplets in the part near the myocardium.

Liver: Chronic passive congestion. Plenty of glycogen in the nuclei of parenchyma cells.

Pancreas : No pathological changes.

Kidneys: Apart from mild arteriosclerosis of the large and middle arteries, no changes.

Adrenal glands: Slight hyperplasia of the cortex, at some areas of nodular type.

Lungs: Beginning bronchopneumonia in block taken from the left lower lobe.

Discussion

It is rather significant that the epileptiform seizures, as described by the patient's family, were interpreted as epileptic fits which made their appearance unusually late in life. Cerebral symptoms are not infrequently an initial and outstanding feature in heart disease. Only close observation revealed the true cause of the attacks: the paroxysmal cerebral ischæmia (Fishberg, 1940) being caused by a severe disturbance of cardiac rhythm on the basis of changing degrees of heart block. This block seems to have passed through several stages; it had apparently been of an intermittent nature, in itself a rare occurrence (Comeau, 1937), in a period before, as well as after, the patient's first stay in hospital—his pulse was 60 in the intervals between attacks; A-V block became " complete " and " established ", as Campbell (1944) puts it, at any rate after the patient's second admission to hospital. Typical Adams-Stokes attacks were observed when his ventricles came to a complete standstill, that is to say, when even the ventricular pacemaker stopped its action or its impulse was prevented from spreading over the ventricles (" block in block " (Schmoll)). The sudden onset of ventricular standstill in a pre-existing complete A-V block is an occurrence that requires explanation. The same theories that have been adopted for intermittent interruptions of A-V conduction apply—besides the changes of vagal inhibition—in these cases also. Some subtle local circulatory deficiency as suggested by Carter and McEachern (1934), may prevent the spreading of impulse over the ventricle. Dubbs (1938) rightly sums up the general state of knowledge by confessing our ignorance of the immediate cause of ventricular asystole that leads to the Adams-Stokes syndrome. In one instance at least, even auricular inactivity was demonstrated by a cardiogram that failed to exhibit any impulse (sinus?) whatsoever, thus surpassing in its negativity as an in vivo finding tracings which have been taken even a considerable time after clinical death. In the patient's last days attacks were observed occurring on the basis of ventricular fibrillation which represents another cardiac condition leading to cerebral ischemia.

The explanation for the occurrence of the cardaic disturbance was usually to be found in the fluctuations of diabetic balance. This relation is borne out, for example, by Fig. 6 showing the incidence of attacks and diabetic balance at the beginning of the patient's stay in hospital. The onset of these paroxysms was usually observed when any irregularity in the treatment of his diabetes occurred (overdose of insulin, hyperglycemia). On the other hand, even a short series of attacks tended to derange completely his metabolism to the hyperglycæmic side, thus provoking a rise to more than 500 mg. per 100 c.c. after an attack which had been caused by an overdose of insulin.

It seemed rather natural to assume that arteriosclerosis, especially of the coronary and cerebral vessels, was the underlying anatomical condition of a man, 58 years old, who had

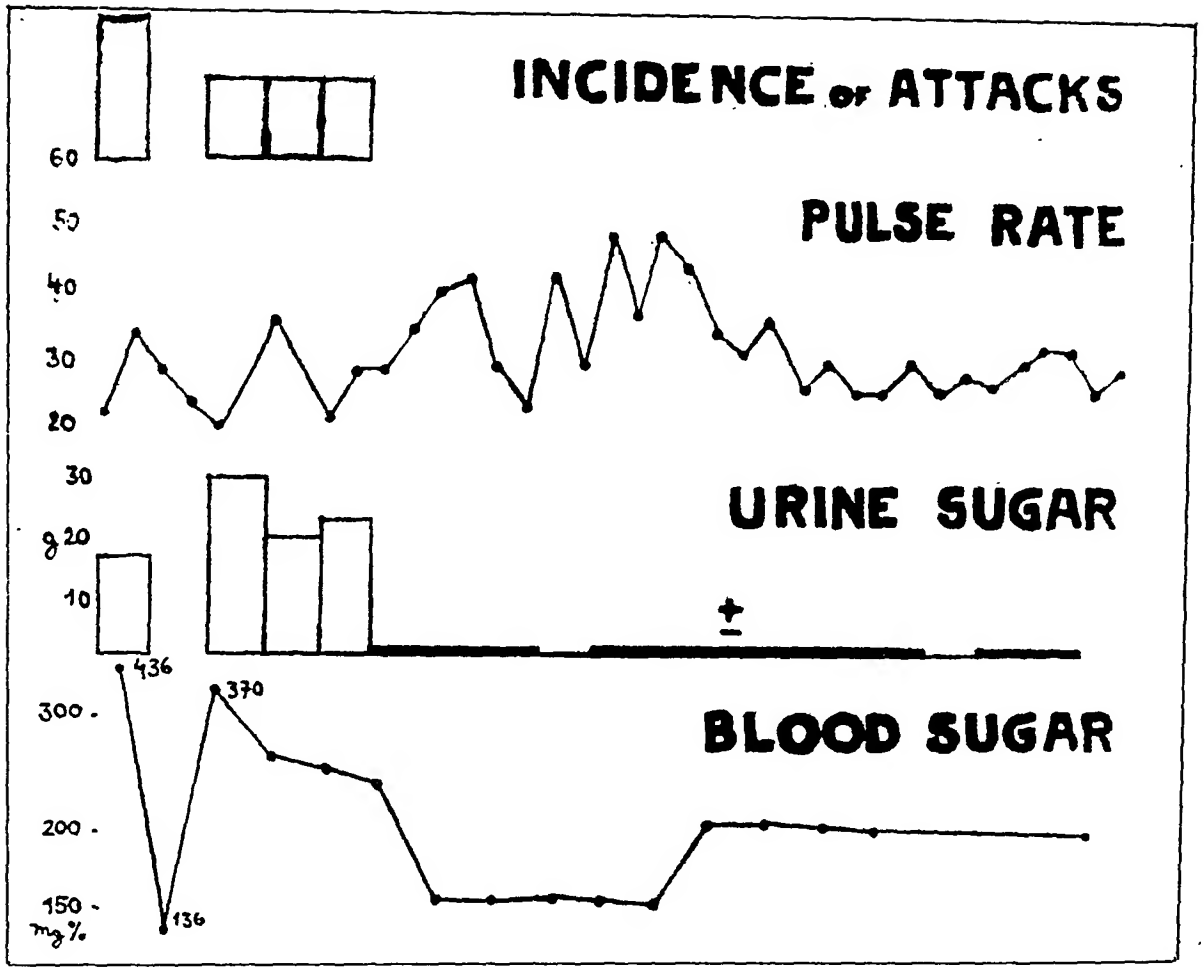

FIG. 6.

been suffering from diabetes for 13 years. Under the circumstances it may be understood that a coronary occlusion was taken into consideration as the possible source of that severe series of attacks provoked by an overdose of insulin the night before his admission to hospital. To our great surprise the findings at autopsy were those of mild arteriosclerosis, in the words of the pathologist, " not even corresponding to the patient's age and by no means explaining the severe disturbances described." In this respect our case bears some resemblance to that of Lawrence and Forbes (1944) suffering from paroxysmal heart block and ventricular standstill, in which post-mortem examination also showed " no gross abnormality of the heart " and the atheromatous changes in the coronary arteries " were not sufficient to obstruct the lumen at any point ". Retrospectively, the absence of the psychic behaviour characteristic of cerebral sclerosis, the absence of retinal signs of this disease, and the lack of anginal pain, should be stressed.

An explanation other than the various changes in the structure and tone of arteriosclerotic vessels must therefore be sought. Taking into consideration the close interrelationship existing between the state of diabetes and the behaviour of the heart, a causal connection between cardiac and metabolic disturbance seems most probable. Under the weight of the overwhelming evidence of arteriosclerosis in diabetics, other mechanisms apt to bring forth such disturbances have been only rarely discussed. A case of transient heart block in a diabetic woman, 56 years old, was reported by Blaisdell (1935). In this case, however, partial A-V block occurred for a short period following coronary thrombosis. Joslin (1940), who lays stress on the " astonishing " frequency of arteriosclerosis as a post-mortem finding in diabetics, mentions also degenerative changes in the myocardium not dependent on coronary diseases as having been noted by a number of writers. Nathanson (1932) describes the finding of a pale, swollen, cloudy heart muscle in most cases of diabetic acidosis and coma. In our case,

who only rarely reached the state of intensive acidosis and for short periods only, a metabolic influence upon the cardio-cerebral regulation, according to the clinical observation primarily on the cardiac regulation, may be suggested in the light of the cases described by Shirley Smith (1943). He assumes " that diabetes exerts a deleterious effect on the myocardium, not only by virtue of coronary sclerosis, but also through direct impairment of the parenchyma of the heart ". The maintenance of a sufficient carbohydrate combustion is, in his opinion, at least as important, if not more so, than the provision of an adequate oxygen supply to the myocardium. Deficient carbohydrate utilization is the only feature common to hyper-and hypo-glycæmia and may so, to a certain extent, explain similar cardiographic patterns (especially of the S–T) observed in both conditions and in the same way the observations made in our patient. The nutritional state of the myocardium in this case may be seriously affected by abnormal composition of the blood feeding it, whereupon its irritability and conductivity may be thrown out of order. This may be true particularly of the A-V conduction system, the metabolism of which is probably more sensitive to these alterations on account of the more embryonic nature of its muscle fibres. Harrison and Finks (1943) analogously point out that " fuel deficiency will tend to produce in the tissues metabolic disturbances similar to those induced by oxygen deficiency ". On the other hand, the fact that the patient could be tided over some lighter attacks simply by diverting his attention may point to a cerebral part in this complicated mechanism, the brain in itself being similarly subject to the disturbances of tissue nutrition produced by metabolic fluctuations. This mechanism finally became completely upset, the correlation between diabetes and cardiac disturbance becoming lost; in this last period, however, satisfactory control of diabetes was no longer obtained; cardiac, metabolic, and cerebral regulations became progressively destroyed.

In accordance with these considerations success and failure as to the appearance of attacks were largely determined by the control of diabetes at the corresponding moment. In this respect therapy was successful for a certain time. As a matter of fact, only insulin and glucose respectively were effective in controlling the seizures. Apart from these two substances a good many drugs were given a trial. Since severe arteriosclerosis, as explained above, was assumed to be the underlying condition, doses of several of them were applied rather cautiously; adrenaline and barium chloride were therefore completely excluded. Atropine, ephedrine, erythrol-tetranitrate, and potassium iodide, were of no avail. Aminophylline sometimes seemed to shorten a series of attacks when given into the vein, and definitely influenced only Cheyne-Stokes respiration. Caffeine was successfully used for resuscitation when injected intracardially; it occasionally seemed to shorten an attack. Oxygen did not abolish the attacks but had, at least for a few weeks, a considerable and interesting effect: during its administration no epileptic convulsions appeared and consciousness was usually not lost completely; the pulse did not entirely disappear, but the periodicity of respiration and cardiac disturbance remained uninfluenced. When oxygen administration was stopped, a violent seizure followed almost immediately. This partially modifying action of oxygen has been observed in a similar way by Miller and Fulton (1941). Digitalis had no effect upon the disturbance of rhythm or on the liability to attacks.

A good deal has been written about the relationship of Cheyne-Stokes respiration to Adams-Stokes attacks. Various different patterns of behaviour have been observed and there is no consensus of opinion regarding the frequency of these conditions together: whereas Wenckebach and Winterberg (1927) or Steele and Anthony (1933) remark on the rarity of this coincidence, Price (1927), for example, considers it as a fairly common combination. In the case of Hamburger, Katz, and Rubinfeld (1931–2) " the change in block synchronized with the change in the character of breathing ". A similar occurrence was the one observed in our case.

The case described represents a rare cardio-cerebral complication in a diabetic, the severity of which is illustrated by the violence of the seizures and by the lethal outcome. It belongs to a category of heart disease which, comprising also, among others, heart disease caused by vitamin deficiency, might be designated as " nutritional heart disease "; a classification that points to the nutrition of the heart muscle being at fault—in our case owing to a disturbance of carbohydrate metabolism.

SUMMARY

A case is reported of complete A-V block in an elderly diabetic in whom post-mortem examination revealed only mild arteriosclerotic changes, especially of the coronary circulation. Many series of Adams-Stokes attacks were observed, accompanied by Cheyne-Stokes respiration. These seizures were mostly caused by ventricular standstill and finally also by ventricular fibrillation. These mechanisms are demonstrated by electrocardiograms; in one instance even auricular stoppage was graphically demonstrated.

As the anatomical findings by no means explain the profound disturbances of cardiac action, and as, on the other hand, it was noted that these attacks usually occurred when diabetic balance was seriously upset, an attempt is made to explain the changes in cardiac behaviour by metabolic fluctuations. It is suggested that these fluctuations interfere temporarily with the normal nutrition of the heart muscle, possibly foremost of the A-V conduction system, whenever hypoglycæmia or hyperglycemia prevails.

The applied treatment is briefly discussed.

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ARTERIAL THICKENING IN OLD AGE

BY

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The pathology of arteriosclerosis has been much studied in recent years: but the clinical aspects have had little attention. A small book on diagnosis written by Parkinson in 1898 had more space devoted to examination of the arteries than Saville's " Clinical Medicine " of 1939, which has six times the number of pages. Even Cowdry's symposium on arteriosclerosis does not say much on the clinical aspects of arterial thickening. In fact, Sydenstricker there quotes the statistics of the Life Extension Institute of America, and gives the final age group as " sixty or over." It is only in this and the following decades that the state of the arteries assumes real importance. It would seem, therefore, that there is a lack of reliable information about the arterial thickening of later life, at least on the clinical side. Apart from a note by Lansbury and Brown about the importance of calcification and the figures of Sydenstricker, there is little in recent papers which bears on this point. The present paper deals with the findings on examination of Chelsea pensioners and offers a new method of classifying arterial thickening in old persons.

STANDARDS

This investigation was one of a series designed to provide data about the normal variations of temperature, pulse rate, blood pressure, arterial thickening, etc., in healthy old persons. Chelsea pensioners, of whom 341 were examined, proved excellent material for this purpose. All were veterans of the old professional British regular army and therefore had been fit, healthy men accustomed to exertion in their early manhood. Before coming to the Royal Hospital, they had to be medically certified as being fit to perform light duties—sick men not being admitted. In addition to being selected material, these men lived a regular life under supervision and medical observation.

Every man in the series under review was given a physical examination, in the course of which his radial, brachial, temporal, and femoral arteries on both side of the body were palpated. The vessels were compressed by the index and ring fingers while the third finger felt the artery and rolled it under the finger-tip. After this, the fingers were rubbed up and down the course of the vessel longitudinally to ascertain the amount of tortuousity or calcification present, as well as the amount of thickening of the wall.

Generally speaking, the brachial arteries showed thickening of their walls more markedly than any others, but calcification was found only in the radial and temporal arteries. Tortuousity was common in the temporal vessels, but also occurred in radials and brachials. In the last two it was associated with at least moderate thickening, which was not the case as regards the temporals. The brachial tortuousity took the form of small segments of a large curve, but the radial curves were often large segments of a small one. Brachial tortuousity was often accompanied by radial calcification. In fact, one group (IV) in the suggested classification was composed of cases showing brachial thickening and tortuousity with slight or patchy calcification of both radials. Examination of the femoral artery gave little additional information as a rule. The fundus oculi was not examined, a previous survey having shown little correlation between the opthalmoscopic picture and the peripheral general arterial state. (Howell, *Brit. Heart J.*, 1942). For classification purposes, the final impression after examining and, if necessary, re-examining the accessible arteries was taken as guide. A few cases were hard to decide, but these mostly had some calcification of one radial with only slight

thickening elsewhere. The classification of arterial changes by age groups is shown in Table I.

TABLE I

ARTERIAL THICKENING IN PATIENTS DIVIDED ACCORDING TO AGE

Age period	Group distribution of each age period in percentages of each age period					
	Total	No. I	No. II	No. III	No. IV	No. V
55–59	3	100	—	—	—	—
60–64	11	27	54	19	—	—
65–69	37	27	19	43	8	3
70–74	146	19	21	48	8	4
75–79	81	8	13	57	15	7
80–84	40	5	10	43	30	12
85–89	20	—	10	40	25	25
90–95	3	—	—	—	—	100
	341					

CLASSIFICATION

Five groups of men were found on analysis of the 341 examined. The first consisted of those without any obvious arterial thickening. The second was composed of those in whom the thickening was slight. The third group, classified as having moderate thickening, had arteries that were easily palpable. The fourth showed thickening of all the arteries examined, with tortuousity in some of them, often accompanied by slight or patchy calcification of the radials. The fifth group had marked calcification present. As may be seen in Table I, there tended to be a steady drift from group I to group V as the age increased. One man, not included in this series, was watched over a period of five years. At the beginning of this time, although his fundus oculi showed arterial changes, there was only minimal thickening of his limb vessels. At the end of the period, he was in group III. Other men observed over a period of three years, passed from group II to group III, from III to IV, from IV to V, and even from III to V during this time. This occurred in ten patients, while ten others remained in the same state as at the beginning of the period. No cases were found to proceed from harder to softer arteries, or from tortuousity to straight vessels, but two doubtful cases were finally settled in group IV, rather than group V.

The first group, those without arterial thickening, was composed of 53 men (Table II), whose ages ranged from fifty-six to eighty-four. Many of the older members did not look their age nor behave in a senile fashion. A few were obese, so that palpation of their vessels was not easy. The vast majority in this group were fit and healthy, only two having physical signs of disease; one had a Plummer-Vinson syndrome, the other had high blood pressure with auricular fibrillation and a large heart.

TABLE II

AGE OF PATIENTS DIVIDED ACCORDING TO GROUP OF ARTERIAL THICKENING

Arterial group	Percentage of each arterial group in each age period				Total	Percentage
	55–65	65–75	75–85	85–95		
I	12	71	17	—	53	15·5
II	10	65	22	3	60	17·8
III	1	54	39	5	159	46·2
IV	—	34	54	12	44	12·9
V	—	24	44	32	25	7·6
					341	100·0

The second group of pensioners comprised 60 men between sixty and eight-five of age. In these cases the arteries could be felt like a thin tape when the vessels were compressed. Any with vessels more prominent than this on palpation were placed in the next group, if more than one artery was affected. The brachials were easier to feel than the radials, while the temporals often had tortuousity, but nevertheless remained soft. The age distribution was similar to that of the preceding class, except that a larger number of men over seventy-five

was met. Only three of the men had a medical history of any significance, two having past cerebral thromboses and one congestive heart failure following hypertension.

The third group was by far the largest. It contained the men with arteries that were thickened, but not tortuous nor calcified. The degree of thickening varied from a sensation as of a soft cord under the skin to that of a tough leathery tube. There were probably several sub-groups not yet clearly defined. The number of cases totalled 159, nearly half the number of men examined. Over 40 per cent of all men between sixty-five and eighty-nine came into this class, but only two were under sixty-five. A great variety of physical states was met in this category of pensioner, varying from perfectly fit healthy old men to those with chronic bronchitis, with old hemiplegia, or with cerebral arteriosclerosis. The younger members of the group were not more clearly healthy nor more conspicuously unfit than their seniors. For this reason it is hard to draw any conclusions about the significance of this degree of arterial change.

The fourth group was composed of 44 pensioners whose ages varied from sixty-six to eighty-nine. More than half the men were over eighty. As the distinguishing feature of the group was the possession of arteries that were thickened and tortuous, with or without slight calcification: it suggests that extreme age, tortuousity, and calcification are connected in some way. The calcification varied from a few hard beads to be felt on rubbing up and down the vessel to irregular hardened areas several millimetres in length. Ten men (23 per cent) in the group were noted as completely fit. The others had signs of past disease or of degeneration such as sclerotic cardiac murmurs, marked effort dyspnœa, hemiplegia, and so on. Some of the pensioners who needed recurrent admissions to the infirmary of the hospital were found here. On the whole, the older men were healthier than the younger ones with this group.

The fifth group included 25 pensioners all of whom showed marked calcification of their radial arteries as well as thickening of their palpable arteries. Their ages ranged from sixty-six to ninety-one, three quarters of them being over seventy-five. All three men over ninety were in this group; but the oldest pensioner in the hospital, aged ninety-six, who was not included in this series, would have been placed in the fourth group. Twelve of the men were relatively healthy and able to get about in comfort. The remainder were more or less infirm, six having only recently returned from the infirmary to which they had been on account of advanced cardio-vascular disease requiring treatment.

Blood Pressure

Each man had a blood pressure reading taken as part of his examination. While a single reading is not satisfactory, it was noted that, in cases where the usual figures for a man were known, there was no deviation from what had been expected. 79 per cent of the pensioners had systolic readings over 160 mm. This was higher than the 50 per cent with similar levels found in 120 successive admissions to the infirmary in 1941–42. The present series, however, deals with the healthy men and not the sick. It was found that in group I, 59 per cent had a systolic pressure over 160 mm.; in group II, 53 per cent; in group III it rose to 80 per cent; in group IV to 84 per cent; and in group V to 96 per cent. The high percentage in the last three groups is noteworthy. About a quarter (24·6 per cent) of the men had their

TABLE III.—Systolic Figures over 200 mm.

Arterial group	Age periods				Total	Percentage of each group with B.P. over 200
	55–65	65–75	75–85	85–95		
I	0	5	1	0	6	11
II ..	0	2	4	1	7	12
III ..	1	24	15	4	44	29
IV ..	0	5	9	2	16	37
V ..	0	3	6	4	13	52
All groups ..	1	39	35	11	86	25
Percentage of each age period with B.P. over 200	7	21	29	50	25	

systolic pressure over 200 mm. In these pensioners, the diastolic figures varied from 100 mm. to 140 mm., only a small number being over 120 mm. Out of a total of 86 patients, 6 were in group I, 7 in group II, 44 in group III, 16 in group IV and 13 in group V. Only 1 was under sixty-five, 39 were between sixty-five and seventy-five, 35 between seventy-five and eighty-five and 11 between eighty-five and ninety-five. These results are shown in Table III.

As may be seen from Tables III and IV, the percentage of men with a systolic figure over 200 mm., rises with age, but later than the percentage of all the men with raised systolic pressure. From these figures it seems that both advancing age and increasingly thickened arteries were associated with a higher blood pressure.

TABLE IV

ARTERIOSCLEROSIS AND RAISED BLOOD PRESSURE (OVER 160)

Arterial group	Age periods				Total	Percentage of each group with B.P. over 160
	55–65	65–75	75—85	85–95		
I ..	1	23	7	0	31	59
II ..	2	19	11	2	34	53
III ..	1	64	54	8	127	80
IV ..	0	13	20	4	37	84
V ..	0	6	10	8	24	96
All groups ..	4	125	102	22	253	77
Percentage of each age group ..	28	68	84	95	77	

DISCUSSION

The first impression arising from the examination of these cases was that the usual procedure of compressing the radial artery at the wrist was not a sufficient guide to the state of the vessels. In some patients there would be neither tortuousity nor calcification in the segment of the artery palpated, and this might give rise to a false estimate of the degree of arterial change present. Examination of both radials and brachials was the minimum which could be of any real value. Also the process of rubbing the fingers up and down the course of the artery gave a lot of information about its condition that was not elicited in any other way. This was especially true when the patient was obese and the vessel not easy to feel. Next, it was found that while there was truth in the general rule that thickening, tortuousity, and calcification grew more frequent with advancing years, yet many exceptions could be met. In fact, there seemed to be a number of men in the eighties whose arteries would not have been abnormal for those twenty years their junior. The group III cases were a real problem. While the proportion of pensioners with raised blood pressure was much higher than in the two preceding groups, and a history of past vascular lesions was not uncommon, yet a number of the men in this group were known to be much more active in body and mind than others of their age. Even among those between sixty and seventy there were about equal numbers of prematurely decrepit veterans and men who were taken for fifteen years less than their true age. The sensation of moderate thickening of an artery covers so many gradations which it is difficult to distinguish that, as stated before, there are probably several sub-groups. As expected, tortuousity and calcification were usual in pensioners over eighty. The ability to express these findings in a simple classification indicates that it has some advantages over the "slight," "moderate," "marked" thickening and "calcified arteries" which are the terms commonly employed at present.

SUMMARY

When the arteries of 341 Chelsea pensioners were examined, it was found that they could be classified into five groups, each with distinct characters; and probably successive stages of sclerotic change. An improved method of clinical examination of arteries is described and its advantages pointed out.

MALIGNANT HYPERTENSION CURED BY UNILATERAL NEPHRECTOMY

BY

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The classical work of Goldblatt (1934 and 1937) and of Wilson and Byrom (1939), demonstrating the development of hypertension following unilateral renal ischæmia and the return of the blood pressure to normal following removal of the renal lesion, gave a great stimulus to the clinical study of hypertension. As a result it is clear that in man, as in the experimental animal, renal ischæmia gives rise to hypertension. If the lesion is confined to one kidney and that kidney is removed before permanent hypertensive changes have developed the hypertension may be cured. Many clinical cases have now been investigated and the commonest cause of unilateral renal disease producing hypertension appears to be chronic atrophic pyelo-nephritis (Braasch, 1942). How this leads to renal ischæmia is not clear but Barker and Walters (1940) have suggested that there may be an obstruction to the renal arteries in these cases. Among other conditions found to produce hypertension have been atherosclerosis of the renal artery, pyonephrosis, renal tuberculosis, neoplasm, and trauma. Apparent cure of the hypertension following removal of the damaged kidney was first reported by Butler (1937) in a case of pyelo-nephritis, and similarly successful results have been reported by others. (Patch, Rhea, and Codnere, 1940; Barker and Walters, 1940; Movin, Ohlsen, and Pedersen, 1944; Powers and Murray, 1942; Platt, 1941, etc.)

Successful reports of nephrectomy have also been made in renal tuberculosis (Kennedy, Barker, and Walters, 1941), in tumour (Koons and Ruch, 1941; Richardson and Smart, 1941), following trauma (Farrell and Young, 1942), and in atherosclerosis of the renal artery (Leiper, 1944).

However removal of the offending kidney has by no means always resulted in cure of the hypertension and in some cases in which the immediate effects of the operation were gratifying the blood pressure later returned to the same level as before operation. In 1940 Schroeder and Fish analysed reported cases and laid down the following criteria for operation.

> The onset of hypertension should be recent.
> The renal lesion should be confined to one kidney and should be such that diminution of function has occurred in that kidney.
> Renal function should be within normal limits.
> Retinitis should be absent.
> Arterial pressure should be persistently elevated.

The whole question has recently been reviewed in detail by Sensenbach (1944) who was only able to find 5 cases in which nephrectomy was successful after two years: he agreed in the main with the above criteria. However the cases reported by Platt (1941), by Kennedy, Barker, and Walters (1941), by Powers and Murray (1942) and by Leiper (1944) show that the presence of papillœdema and retinitis (malignant hypertension) is by no means a contra-indication to nephrectomy.

The object of this paper is to report two cases of this type in which the hypertension was apparently cured by unilateral nephrectomy.

Case Notes

Case 1. A man, aged 32, was admitted to hospital on February 2, 1942, with attacks of severe headache and vomiting for about two months. These attacks came on about once a week and his sight gradually became blurred in the left eye. He had had occasional headaches from January till September 1941 when he was discharged from the R.A.F. on account of " low mentality and lack of confidence." In September 1941 he had a sudden severe pain in the left loin, which lasted three days and was so bad that he could not stand. On admission to hospital the blood pressure was 210/130. Both fundi showed papillœdema and small exudates; this was more marked in the left eye which showed a macular star. There was no clinical or radiological evidence of cardiac enlargement. The urine contained a trace of

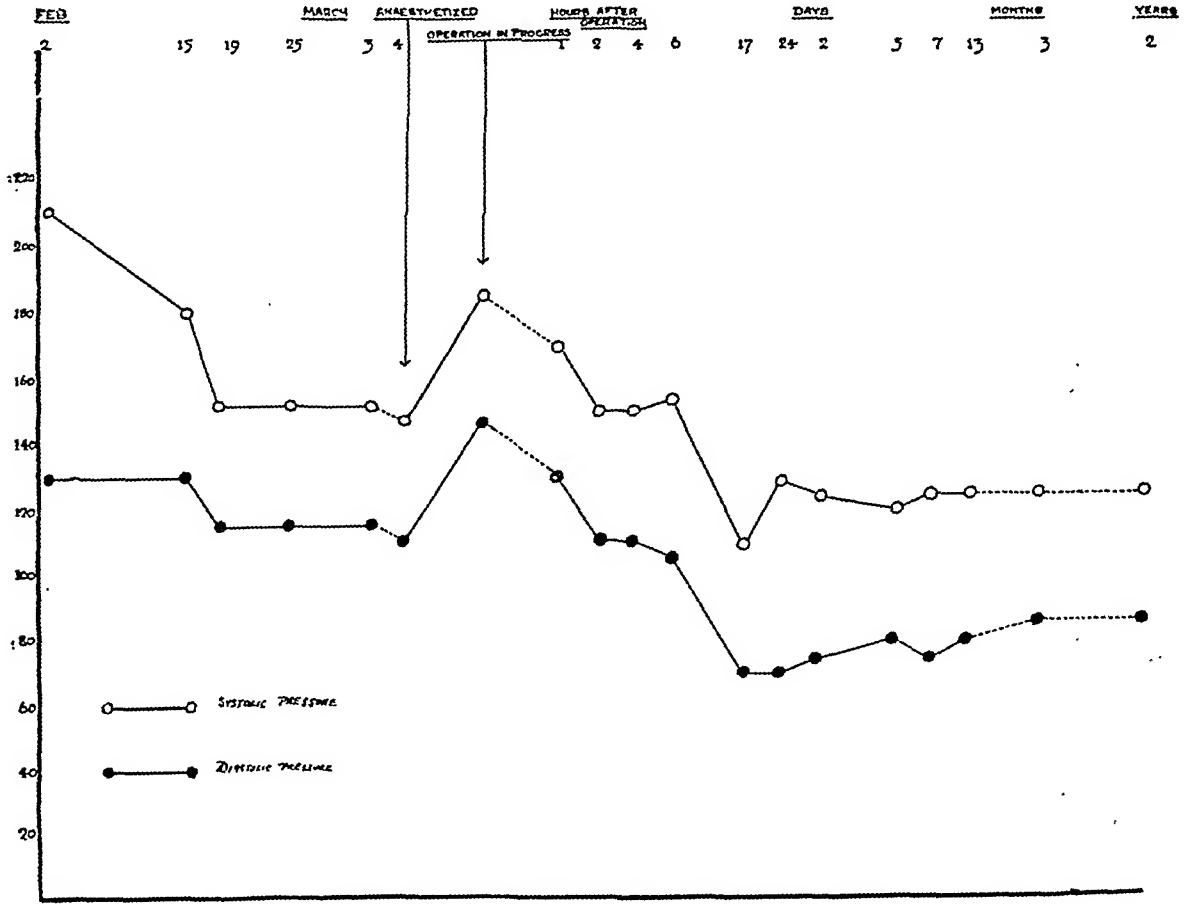

FIG. 1.—Blood pressure readings in Case I.

albumen, but no cells or casts were seen in the centrifuged deposit. Blood non-protein nitrogen was 45 mg. per 100 c.c. The urea concentration in the urine after 15 g. of urea was 2·8 per cent after 1 hour, 2·5 per cent after 2 hours, and 2·4 per cent after 3 hours.

Intravenous pyelography showed very poor excretion of dye on the left side. Cystoscopy showed no abnormality in the bladder, but no dye was excreted from the left ureter 15 minutes after injection, although excreted in 5 minutes from the right side. An ascending pyelogram showed small shrunken calyces on the left side. With rest in bed the blood pressure fell slightly but still remained elevated.

On March 4 a left nephrectomy was performed by Mr. FitzGibbon. The blood pressure fell to normal (115/70) seventeen hours after the operation and was still normal when last seen two years later (125/85). The retinal lesions have steadily improved, the papillœdema and exudates clearing up completely. Vision is still impaired in the left eye.

The pathological report on the kidney is as follows:—" The kidney weighs only 75 grams. This reduction in size is due to the presence of several old infarcts. There is a rim of fresh hæmorrhage just beneath the capsule; presumably due to trauma at the time of operation.

The renal vessels have been divided close to the hilum and the cut ends showed no apparent gross lesion. The pelvis of the kidney gives no sign of dilatation or infection.

Histologically several sections show old healed infarcts but an interesting feature is the presence of large areas of relatively ischæmic kidney tissue, with viable glomeruli lying in a fibrous matrix containing shrunken tubules. One branch of the renal artery, just within the hilum of the kidney, shows a remarkable lesion in its wall. The lumen is patent but narrowed by subintimal fibrosis and between the media and the external elastic lamella is a vascular scar containing some grains of hæmosiderin. This may well represent a healed lesion of polyarteritis nodosa."

Case 2. A Jugoslav merchant seaman, aged 20, was admitted to hospital on February 28, 1944, complaining of severe headache and increasing failure of vision. These symptoms had been present for four months. He had been invalided home from Algiers where he had

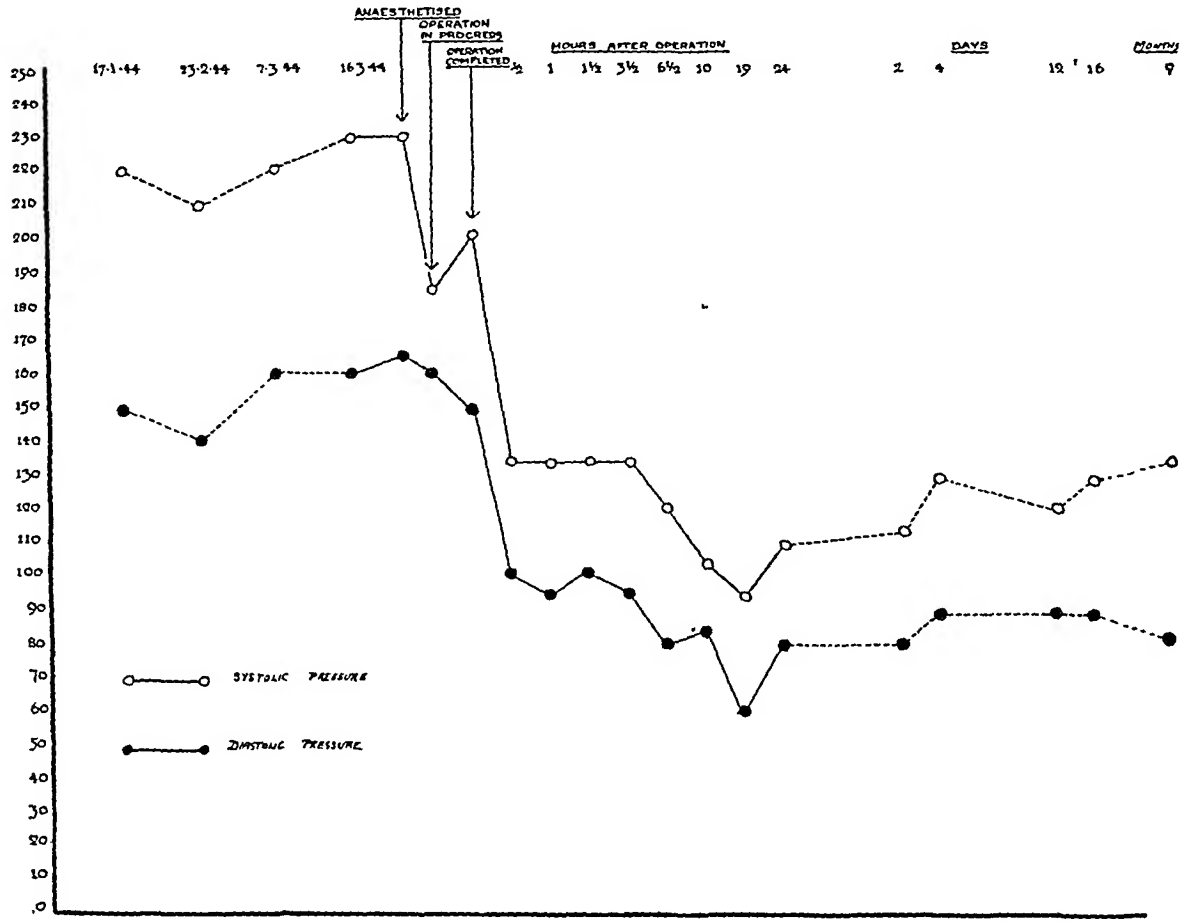

FIG. 2.—Blood pressure readings in Case 2.

been in hospital with infective hepatitis. There his blood pressure was found to be 225/145, the urine contained albumen and a few hyaline casts and the blood urea was 30 mg. per 100 c.c. Five months before he had malaria at Taranto. On admission his blood pressure was 210/140. There was no clinical or radiological evidence of cardiac enlargement. The urine had a specific gravity of 1020, contained a trace of albumen and a few hyaline casts, but was otherwise normal. Blood urea was 40 mg. per 100 c.c. After a litre of water the urine specific gravity fell to 1002 and with restricted water it rose to 1020. There was hypertensive retinopathy more marked in the right than in the left eye. Both discs showed severe papillœdema; the retinæ showed hæmorrhages and white exudates and a macular star. Intravenous pyelogram showed no dye excreted on the left side. Cystoscopy showed a normal bladder with poor flow of turbid urine from the left ureter. No dye was excreted from the left kidney 15 minutes after injection but was excreted in 5 minutes on the right side. An ascending

pyelogram showed a small pelvic shadow on the left side. Rest in bed produced no definite fall in blood pressure.

On March 16 a left nephrectomy was performed by Mr. Cooke. The blood pressure had fallen to 140/100 on return to the ward from the theatre and 19 hours later was 95/60: the next day it rose to 115/80 and on discharge was 130/90. Five days after operation the papillœdema had subsided considerably. It has not been possible to examine this patient again but a report from the Henry Radcliffe Convalescent Home nine months later states that his blood pressure is 135/80.

The pathological report on the kidney is as follows. " The kidney is much reduced in size, weighing only 51 grammes and measuring 8 by 5 by 2·6 cm. The kidney shape is maintained. The capsule strips easily revealing a perfectly smooth surface with no scars or hæmorrhages, but with a small, depressed, yellow infarct at the lower pole; this infarct subtends an area on the surface about 3 mm. square. The vessels are cut off close to the hilum but careful examination deep into the kidney shows no gross lesions in arteries or veins; the arteries have soft thin walls. Histological examination shows that the reduction in size of this kidney is due to a general shrinkage of the epithelium of all the renal tubules. The vessels and the glomeruli are unchanged. The general shrinkage of kidney tissue is what one would expect with partial occlusion of the renal artery; this view of the ætiology gains some support from the presence of an old infarct. The part of the renal artery left attached to the aorta probably bears the cause of the condition."

Summary

Two cases are described, apparently showing complete cure of malignant hypertension following unilateral nephrectomy. In one the renal lesion appeared to be due to infarction but in the other the cause was not determined.

My best thanks are due to the two surgeons, Mr. G. M. FitzGibbon and Mr. R. V. Cooke, who performed the nephrectomies and to Professor T. F. Hewer for the reports on the kidneys.

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CARDIAC OUTPUT IN A CASE OF PERICARDIAL EFFUSION
WITH A NOTE ON PERICARDIAL PAIN

BY

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The mechanism of cardiac failure in pericardial effusion, which is generally accepted, is derived from the classical experiments of Cohnheim (1889) and Starling (1897) on the effects of injection of oil into the pericardial sac in dogs. They showed that at first the venous pressure rose parallel with the increasing intra-pericardial pressure, the arterial pressure remaining unchanged. When higher intrapericardial pressure was induced, it began to approach the venous pressure, and at this stage a progressive fall in arterial pressure began and continued until the circulation ceased. They explained these observations by supposing that blood was dammed back in the venous system so that cardiac output fell, the arterial pressure being at first maintained by arteriolar constriction, but failing when the fall in output became extreme. No actual measurements of cardiac output were made. The expression "cardiac tamponade" is derived from this conception of obstruction of the venous inflow to the heart.

Kuno (1917) showed that there was a fall of cardiac output with increasing intrapericardial pressure in a heart-lung preparation, but his results are not applicable to the intact animal since he maintained the venous pressure at a constant level throughout his experiments.

Very few observations on circulatory dynamics in pericardial effusion in man have been made. Katz and Gauchatz (1924) made a detailed study of the mechanism of pulsus paradoxus, and showed that the waning of the pulse beat was due to defective filling of the heart during inspiration. Burwell and Strayhorn (1932) and Resnik, Friedman, and Harrison (1935) have measured cardiac output by respiratory techniques in patients with concretio cordis: they showed that it is low, and rises after operative release of the heart. These conclusions are not, however, applicable to cases of pericardial effusion. Recently an opportunity arose of studying cardiac output and right auricular pressures by means of the cardiac catheter (McMichael and Sharpey-Schafer, 1944*a*) with simultaneous measurement of intrapericardial pressure in a case of malignant pericarditis with effusion.

Case History A manageress of a canteen, aged 32, had noticed a painless swelling in the right breast for two years, but had remained in good health till three weeks previously, when she began to become breathless on exertion. During the previous week she had been breathless at rest and her ankles had swollen.

On examination on 24/11/44 she was of normal build. She had severe dyspnœa at rest with orthopnœa. She had a carcinoma of the right breast involving the skin, with secondary enlargement of the right axillary glands and œdema of the right arm. The jugular veins were distended up to 3 cm. above the sternal angle. The cardiac impulse was diffuse, with maximal pulsation in the fifth interspace, 4 inches from the midline. The sounds were normal, but loud and soft beats alternated. There was pulsus paradoxus at the wrist. B.P. 122/88. There were scattered rhonchi in both lung fields with signs of effusion at the right base. The liver was enlarged to 4 cm. below the costal margin. There was slight pitting œdema of both ankles.

An X-ray of the chest showed general cardiac enlargement, with opacity of the right costophrenic angle. An electrocardiogram (Fig. 1) showed electrical alternation with inversion of T in all leads.

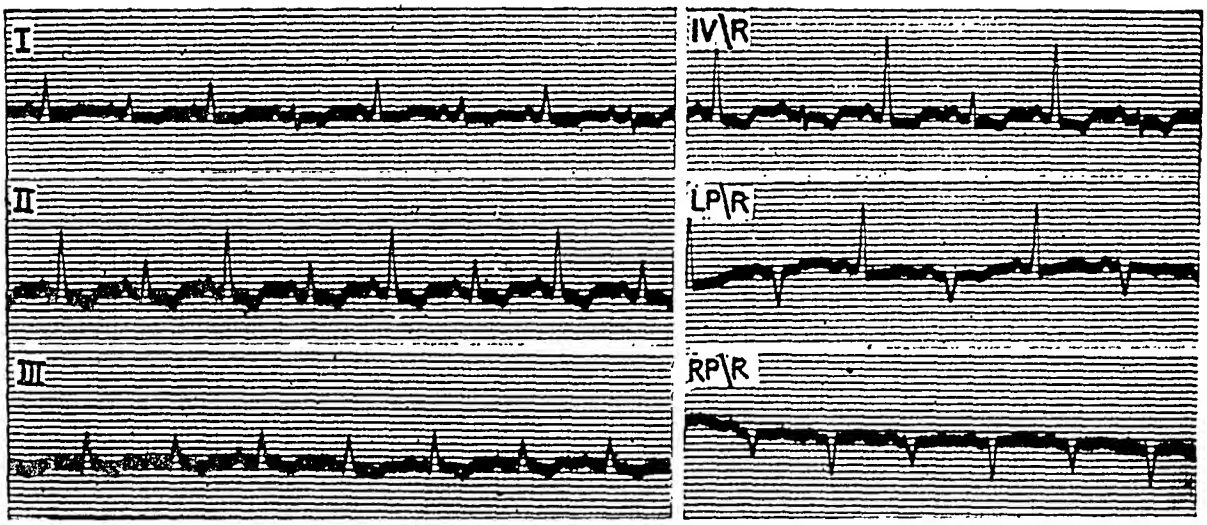

FIG. 1.—Electrocardiogram showing inversion of T in all leads and electrical alternation.

Blood count: Hb. 101 per cent; Red blood cells 5·3 million; white blood cells 11,000.

The diagnosis was malignant pericarditis with effusion.

On 26/11/44 the jugular veins were distended to the angle of the jaw. The patient developed pain in the left chest and a friction rub was heard. Later she had a small hæmoptysis. Digoxin 1·5 mg. was given intravenously. The jugular venous distension fell to a level of 3 cm. above the sternal angle, but there was no clinical improvement.

On 28/11/44, with the patient propped up in bed at an angle of 45° from the horizontal, a cardiac catheter was passed up the left antecubital vein and its tip was located in the right auricle by X-ray. It was connected with a citrate manometer. The right auricular pressure stood at the high value of 15 cm. above the sternal angle. (Normal about 6 cm. below the sternal angle in this position.) There was slight variation in the pressure during the next 30 minutes, but 15 cm. was the average level. The cardiac output was 4·1 litres a minute, which is a low normal figure. A needle was then inserted into the pericardial sac in the fourth left interspace in the mid-clavicular line and was connected to a citrate manometer. The intrapericardial pressure was 7 cm. above the sternal angle. During the next twenty minutes 100 c.c. of heavily blood-stained fluid was allowed to run out of the pericardial sac. At the end of the period the right auricular pressure had fallen to 9 cm. and the intrapericardial pressure to 2 cm. above the sternal angle. Ten minutes later the cardiac output was 3·95 litres a minute (see Fig. 2). During the period of these observations the pulse rate was 124 a minute. The blood pressure was difficult to estimate owing to the œdema of the right arm. The systolic pressure was 122 mm. The diastolic pressure could not be measured satisfactorily but appeared to be 100 mm. After the pericardial aspiration the patient showed a temporary improvement, but then became more dyspnœic, and died five hours later.

In the course of the experiment an incidental observation was made which is of interest. The citrate solution in the manometer was found to be irritant when it escaped into the subcutaneous tissues during the insertion of the catheter (an acid citrate solution, *p*H.4, having been used unwittingly). Each time the manometer was attached to the pericardial needle some of this citrate entered the pericardium and on each occasion the patient complained of pain localized to the outer border of the left upper arm.

Post-mortem, the pericardial sac was distended with 500 c.c. heavily blood-stained fluid. There was a miliary dissemination of secondary deposits throughout the body. There was a large secondary deposit at the root of the pulmonary artery involving the pericardium, which was the source of the hæmorrhagic effusion. The myocardium showed no naked eye evidence of secondary deposits. There was bilateral sero-sanguineous pleural effusion and a large infarct in the left lung.

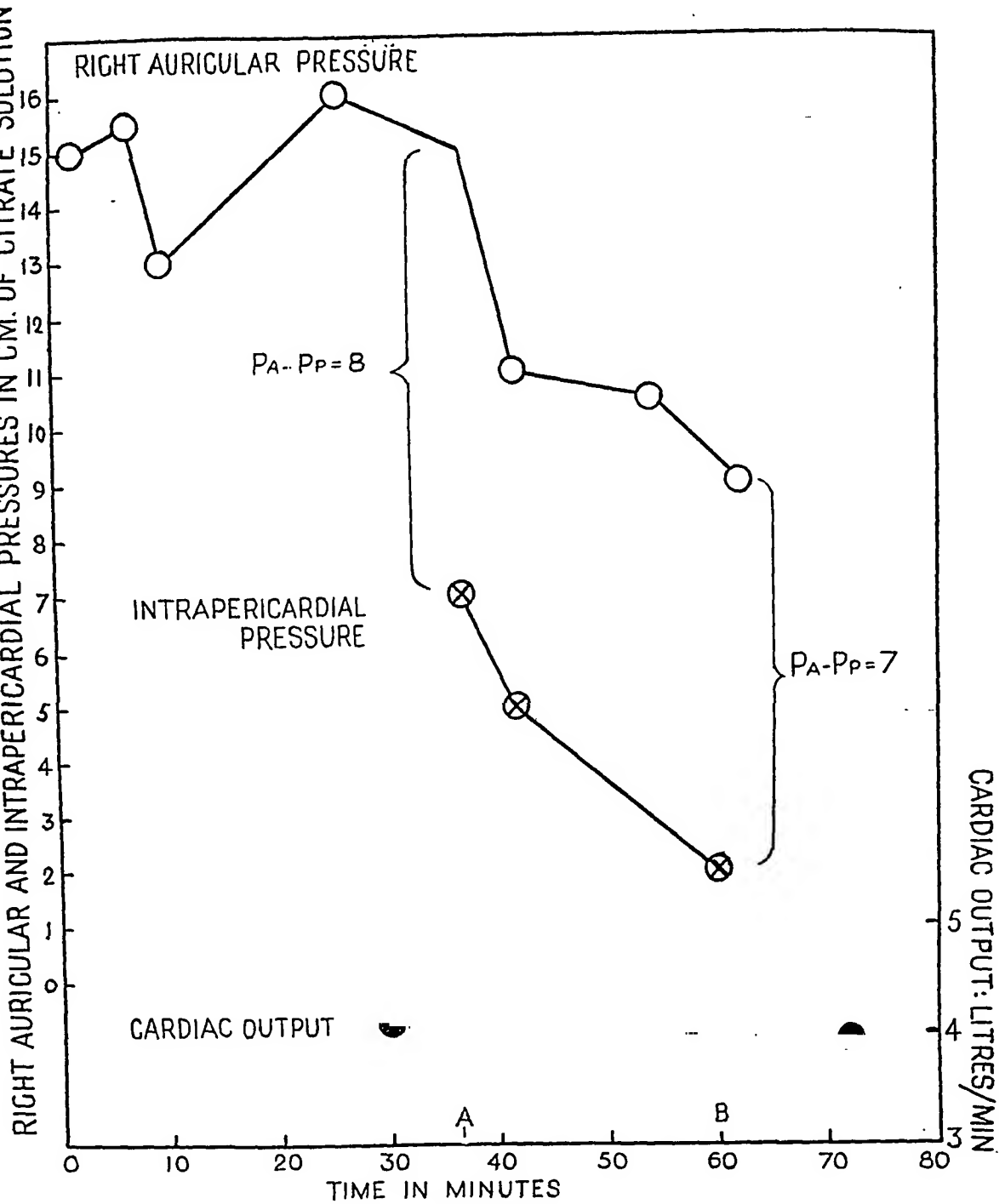

FIG. 2.—Effect of pericardial paracentesis on right auricular and intra-pericardial pressures and on cardiac output. *The high right auricular pressure falls as the intrapericardial pressure is lowered by paracentesis.* Thus the difference between the two pressures (P_a–P_p), which represents the filling pressure of the right auricle is not significantly altered. Cardiac output before and after paracentesis is also unaltered. Between A and B on the base line 100 c.c. of fluid were removed from the pericardial sac.

COMMENT

One of the most important factors that influence cardiac output is the pressure under which the auricle fills. This filling pressure is the difference between the right auricular pressure and the pressure on the outside of the heart. The normal hydrostatic intra-auricular pressure has been measured by Richards, Cournand, Darling, Gillespie, and Baldwin (1941) in six normal subjects and was found to vary between +6·1 and +0·8 cm. of saline with an average of +3·7 cm. The normal mean intrathoracic pressure is also a variable quantity,

but probably averages −6·0 cm. saline (−4·5 mm. Hg., Best and Taylor, 1943). Thus the normal filling pressure of the right auricle has a wide range, but averages +9·7 cm. of saline. In this case of pericardial effusion the filling pressure of the right auricle could be derived from the difference between the right auricular pressure and the intrapericardial pressure ($P_a - P_p$). Before the pericardial fluid was removed it was +8 cm. saline, which is a figure well within normal limits (see Fig. 1). After the fluid was removed the filling pressure was practically unaltered, standing at +7 cm. saline. Associated with this normal and unaltered filling pressure the cardiac output was within normal limits and was also unaltered.

A single observation such as this provides an unsound basis on which to draw any conclusion about the circulatory dynamics in pericardial effusion, but it is interesting to find cardiac output well maintained in a case where the clinical picture was one of cardiac tamponade and to find no alteration in the output when the " tampon " was removed. The output is apparently maintained by the rise of venous pressure, which provides a normal filling pressure for the right auricle. It is clear that any therapeutic measure that may lower the venous pressure, such as venesection or digitalization (McMichael and Sharpey-Schafer, 1944*b*) is contra-indicated. In this case digitalization was certainly of no benefit, although it resulted in no obvious harm. With an increasing effusion, the pericardial pressure will eventually begin to approach the venous pressure, as Cohnheim showed. The output will then fall and the circulation will ultimately come to a standstill. This is presumably what happened terminally in this case, since the pericardial sac was distended with blood-stained fluid post-mortem.

Summary

A case of malignant pericarditis with effusion, presenting the clinical picture of " cardiac tamponade " is described.

Measurements of right auricular and pericardial pressure and cardiac output revealed a right auricular filling pressure and cardiac output within normal limits.

Paracentesis of the pericardium produced a parallel lowering of right auricular and pericardial pressures, so that the right auricular filling pressure remained unaltered. The cardiac output was also unaltered

The suggestion is made that it is only in the agonal stages of cardiac tamponade that the pericardial pressure approaches the venous pressure and that cardiac output begins to fall.

In this case irritation of the pericardium produced pain on the outer border of the left upper arm.

I wish to thank Dr. J. McMichael for his assistance in making these observations.

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TUBERCULOUS PERICARDITIS WITH EFFUSION

BY

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This paper deals principally with effusive (rather than constrictive) tuberculous pericarditis, with special reference to a small series of cases that have come under my care since 1941. There is a general belief that tuberculous involvement of the pericardium is very rare, at any rate in clinical practice. In view of the widespread distribution of pulmonary tuberculosis it would appear surprising that the pericardium should be so seldom attacked by the tubercle bacillus and it is of interest to ascertain whether this is, in fact, the case. My impression is that there has been a tendency to neglect tuberculous pericarditis, and to regard it as unduly rare, almost always fatal, and difficult to recognize in the living subject. I hope to show that, in fact, even acute forms of this disease may not necessarily be fatal and that healed tuberculous pericardial effusions may be a not uncommon cause of constrictive pericarditis.

Reported cases and personal communications from morbid anatomists with wide experience of tuberculosis suggest that a diagnosis of rheumatic or idiopathic pericardial effusion (or polyserositis) is made when, in fact, as with a neighbouring pleural effusion, the causative agent is really the tubercle bacillus. Holmes Sellors in his Hunterian lecture (1944) on constrictive pericarditis, not yet published, has emphasized the close relationship of tuberculosis and constrictive pericarditis.

Incidence. It has also been suggested that tuberculosis may follow hard upon rheumatic fever as a cause of pericarditis and that the condition is quite frequently overlooked clinically. Osler (1893) in 1000 autopsies reported 215 cases of tuberculosis in 7 of which (i.e. 0·7 per cent) tuberculous pericarditis was discovered. Norris (1911) in 7219 cases of tuberculosis from Philadelphia hospitals reported 1780 cases of tuberculosis of which 82 (1·1 per cent) had pericardial involvement. Harvey and Whitehill (1937) state that during 45 years 95 cases of tuberculous pericarditis were admitted to the Johns Hopkins Hospital: of these 71 were clinically important, 37 were proved tuberculous, and 34 were unproven, but these resembled in every respect the proven cases; it should, however, be noted that while the death rate of the proven cases was 83 per cent, of the unproven it was only 6 per cent. No other known cause, apart from tuberculosis, was established in the unproven cases. Cultures of the pericardial fluid were sterile but it is, of course, well known that tuberculous pleural effusions are not infrequently sterile on culture. Kornblum, Bellet, and Ostrum (1933) report an incidence in general autopsies of about 1 per cent, while in patients with pulmonary tuberculosis the autopsy incidence of pericardial involvement was 4 per cent. Gloyne informs me that in an analysis of 200 consecutive tuberculous autopsies which he made for Professor Lyle Cummins to compare with primitive tuberculosis in the Rand Native miners only one case was found in this series, as compared with 31 cases in the latter. Suzman (1944) analysed 1893 autopsies at Guy's Hospital and found that of the 102 tuberculous cases 6 (i.e. 6 per cent) had pericardial involvement.

Pathology. As regards the pathology we may recognize three main stages: (1) acute fibrinous (although commonly rheumatic); (2) effusive pericarditis with pericardial thickening; here if the amount of fluid is great there is extensive pressure on the surrounding structures, viz. the lungs, mediastinum, superior and inferior vena cava, mouths of the hepatic veins, together with dangerous pressure on the heart itself and great vessels within the pericardial sac (cardiac

tamponade); large effusions without any appreciable cardiac enlargement are usually tuberculous, and the amounts may vary from 200–3000 c.c.; and (3) constrictive pericarditis (Pick's disease), the effusion having gradually subsided, leaving a greatly thickened pericardium (the effusions become smaller, thick and at times apparently, but not actually, purulent and then go on to fibrocaseous disease). If the condition is survived the adhesive process may progress to a complete obliteration of the sac with the eventual disappearance of the tubercles and caseation, the final result being an apparent non-specific chronic fibrous adhesive pericarditis. It can, therefore, be stated that in the absence of other causes constrictive pericarditis of a so-called non-specific type is probably tuberculous. Holmes Sellors has confirmed a tuberculous ætiology in most of the cases he has studied (i.e. 8 out of 9), and, as he points out, it may be deduced as axiomatic that rheumatic fever, including pericarditis, never produces the constrictive factor.

A primary tuberculous pericarditis may be regarded for all practical purposes as non-existent. Tuberculosis may reach the pericardium (a) by the blood stream, as part of a miliary tuberculosis, or (b) by direct extension from a mediastinal focus. Study of reported cases and autopsy results suggest that the latter is the more likely and generally accepted means of secondary involvement of the pericardium, the infection taking place by extension along the lymphatic channels between the mediastinal glands and the pericardium. This was indisputably so in my own case of tuberculous pericardial effusion and pulmonary tuberculosis which came to autopsy, and in the autopsy report of a case of pericarditis by Barrett and Cole (1944). Direct extension from the lungs or pleura is almost unknown, which would explain the rarity of pericardial involvement without accompanying mediastinal gland involvement.

It seems probable, as Pagel (personal communication) has suggested, that most cases of tuberculous pericarditis occur in the course of an early dissemination following primary infection. The increase in late primary infection corresponds as he suggests with the contemporary rise in the incidence of tuberculous pericarditis in young adults. Cases occurring in the higher age groups and in senile tuberculosis are probably secondary to a tuberculous mediastinal gland involvement with a recrudescence of an early tuberculous process in the glands.

Symptomatology and physical signs of tuberculous pericarditis. These have been admirably described by many observers (Harvey and Whitehill, 1937, Hanneson, 1941, etc.) and I shall confine my attention purely to some points of particular value in clinical diagnosis. Unlike the rheumatic type of the disease the onset tends to be insidious rather than abrupt. There is seldom any considerable degree of local upset: lassitude, asthenia, and a slight evening temperature may be the principal general manifestations. Dyspnœa is not a pronounced characteristic in the cases reported, nor was it in my own cases, unless the effusion is a massive one, and in one such of my own series the patient would not admit to breathlessness and had been at work with this massive effusion right up to the time I saw her. Pain is present in varying degrees of intensity, bulging of the præcordium is noticeable, and there is frequently a cough (due to pressure on the trachea or bronchi), mostly non-productive, but if pulmonary tuberculosis is co-existent there is usually some sputum. In fact, as occurred in one of my own cases, the cardiac complications can be easily overlooked from a clinical standpoint. Often there is no œdema, but when it is present it frequently appears as a terminal event in massive effusions. With the more massive effusions, engorgement of the neck veins, invisible apex beat, diminished expansion, especially of the left hemithorax, together with a bulging of the epigastrium due to liver depression, as I shall describe later in Case 4, may be seen on inspection. Pericardial friction may sometimes be felt at the base of the heart and a palpable apex beat in the normal position may suddenly diminish or disappear as the effusion increases in size. Percussion may reveal a marked increase in the relative cardiac dullness to the right and left—diagnostically this is of the utmost significance. Auscultatory phenomena of distant heart sounds and a friction rub, even on occasions with a large effusion (especially if adhesions are present), may be heard.

An outstanding feature of effusive or even constrictive pericarditis is the complete absence of significant murmurs, particularly noteworthy in view of the apparent size of the heart.

The so-called Ewart's sign, associated with pulmonary compression with bronchial breathing and whispering pectoriloquy at the angle of the left scapula, is sometimes heard. It was present in two of my cases.

A low arterial and pulse pressure and high venous pressure with a quietly acting heart and a paradoxical pulse (radial pulse almost disappearing on deep inspiration) may occur, especially with massive effusions and those going on to the stage of constrictive pericarditis. The so-called Beck's triad in acute and chronic compression is noteworthy. In acute cardiac compression (tamponade) with massive pericardial effusion Beck describes (1) a low arterial pressure, (2) a high venous pressure, and (3) a quiet heart, although Volhard refers more accurately to a small heart. In chronic cardiac compression (constrictive pericarditis) there is (1) ascites and a large liver, (2) high venous pressure, and (3) a quiet heart. This syndrome must not be confused with a polyserositis, i.e. Concato's disease, but it may be consequent upon it (Paul White), as in my own fourth case. Thus, as emphasized by White (1935), Hanneson (1941), and Sellors (1944), polyserositis as a cause rather than effect of constrictive pericarditis is well recognized, but the conditions may merge imperceptibly into each other. With the development of constrictive pericarditis the low arterial pressure becomes associated with a pulse pressure as low perhaps as 20.

X-ray examination of the heart. This is often the only reliable means of early diagnosis and from this point of view we owe much to the comprehensive study of Roesler, to which those interested are referred. With moderate-sized effusions the cardiac silhouette presents a pear-shaped outline in the erect position, the shape changing in the recumbent position to a globular or rectangular appearance. This change in shape with change in position may be of considerable diagnostic significance as will be shown from a description of one of my cases. Fluoroscopy further assists in the diagnosis from gross cardiac enlargement by demonstrating the presence of diminished or even absent cardiac pulsation, both in massive effusive pericarditis and in constrictive pericarditis. Kymography, when available, gives a valuable permanent record of these fluoroscopic findings and Sellors reported it to be of considerable diagnostic value in one of his cases.

Electrocardiographic examination may, as a general rule, be of diagnostic value, often closely resembling that of an acute myocardial infarction with characteristic changes in the R–T segments, in the T waves, and with the low voltage curves in all leads. Unlike myocardial infarction, however, the Q wave is not exaggerated and the direction of the R–T segment and the T waves are the same in all leads.

Diagnostic pericardial puncture. The one infallible diagnostic procedure is the recovery of pericardial fluid by paracentesis, and this can be safely adopted where symptoms, signs, and X-ray examination indicate it. The correct diagnosis is conclusively determined in pericardial as in pleural effusions—and with equal facility—by pericardial puncture. Pericardial paracentesis is always advisable both for diagnostic purposes and to relieve pressure; if excessive some 300–400 c.c. or more may be removed and replaced by half the quantity of air (gas replacement).

The site usually selected is the fifth left interspace outside the apex beat if this is palpable and just over 1 cm. within the outer border of cardiac dullness. Preliminary adequate anæsthestization with 2 per cent novocaine of the skin subcutaneous tissue right up to the pericardium is essential for success, exactly as it is in the case of pleural effusions. Occasionally, where examination shows more fluid to the right or posteriorly at the angle of the left scapula, a site at the fourth right interspace or posteriorly at the angle of the left scapula may be chosen. A 20 or 50 c.c. two- or three-way syringe is valuable if it is proposed to induce a pneumopericardium, and the type of needle used for pleural punctures is adequate as a general rule, unless the fluid is of a thick consistency and the pericardium is thickened, when a wide-bored needle may be essential.

Induction of an artificial pneumopericardium. This measure was first reported by Wenckebach in 1910, and is particularly indicated for large effusions that require repeated tapping on account of rapid re-accumulation of fluid. The fluid is usually replaced by half the quantity of filtered air. Apart from the symptomatic relief my impression that the re-accumulation of fluid is thereby retarded is reinforced by the course of events in one of my own cases. The

chief therapeutic advantages of this procedure may be regarded as the prevention of rapid re-accumulation of the fluid, the prevention of the formation of adhesions by keeping the pericardium distended with air although this is a doubtful sequence, and the demonstration of the size of the heart which is found to be invariably enlarged with a rheumatic lesion and normal or only moderately enlarged with a tuberculous lesion (see Fig. 7B).

Prognosis. The prognosis of pericardial effusions is naturally dependent upon the nature of the effusion, i.e. whether it is clear, hæmorrhagic, or purulent. Most massive clear effusions and some hæmorrhagic ones are tuberculous.

The mortality rate has hitherto been regarded as very high but recent experiences are certainly suggesting modification of this view. In the same way that it is often difficult to recover the tubercle bacillus from clear pleural lymphocytic exudates, which are sterile on culture (now almost universally recognized as tuberculous in young subjects) so with pericardial exudates similar difficulties present themselves. The general impression is that if tubercle bacilli are readily obtained from the pericardial fluid the prognosis is a grave one (Harvey and Whitehill, 1937). In my fatal case the pericardial fluid abounded with tubercle bacilli. Even guinea-pig inoculations are not always successful in isolating the tubercle bacillus, e.g. Suzman (1944) reported a case of tuberculous pericardial effusion, proved at autopsy, where, during life, the fluid was repeatedly sterile on culture, the Mantoux negative, and a guinea-pig test negative on two occasions. Sellors (1944), in a young girl with a massive tuberculous pericardial effusion found on paracentesis that the fluid was negative for tubercle bacilli. Culture and guinea-pig inoculation were likewise negative yet at operation for pericardial resection a few weeks later the pericardium—of the bread and butter type—was found to be riddled with tuberculous lesions.

Barrett and Cole (1944) report a case where the fluid was sterile on culture and where, when it was injected into a guinea-pig the animal maintained health for the unusually long period of five months. Subsequently it died, exhibiting tuberculosis.

In two unproven cases from my own series the fluids injected into guinea-pigs (killed three months after inoculation) were negative but in every way characteristically tuberculous. As far back as 1917, Parkinson (personal communication) reported a case of proved tuberculous pericardial effusion, which I shall quote in greater detail later, where repeated examinations of the pericardial fluid were sterile on culture.

It is therefore obvious that, from the pathological point of view, a negative fluid by no means excludes tuberculosis. On the contrary, where, in spite of a negative fluid, everything else points to the diagnosis of a tuberculous lesion, my impression has been that the prognosis may be regarded as correspondingly more favourable.

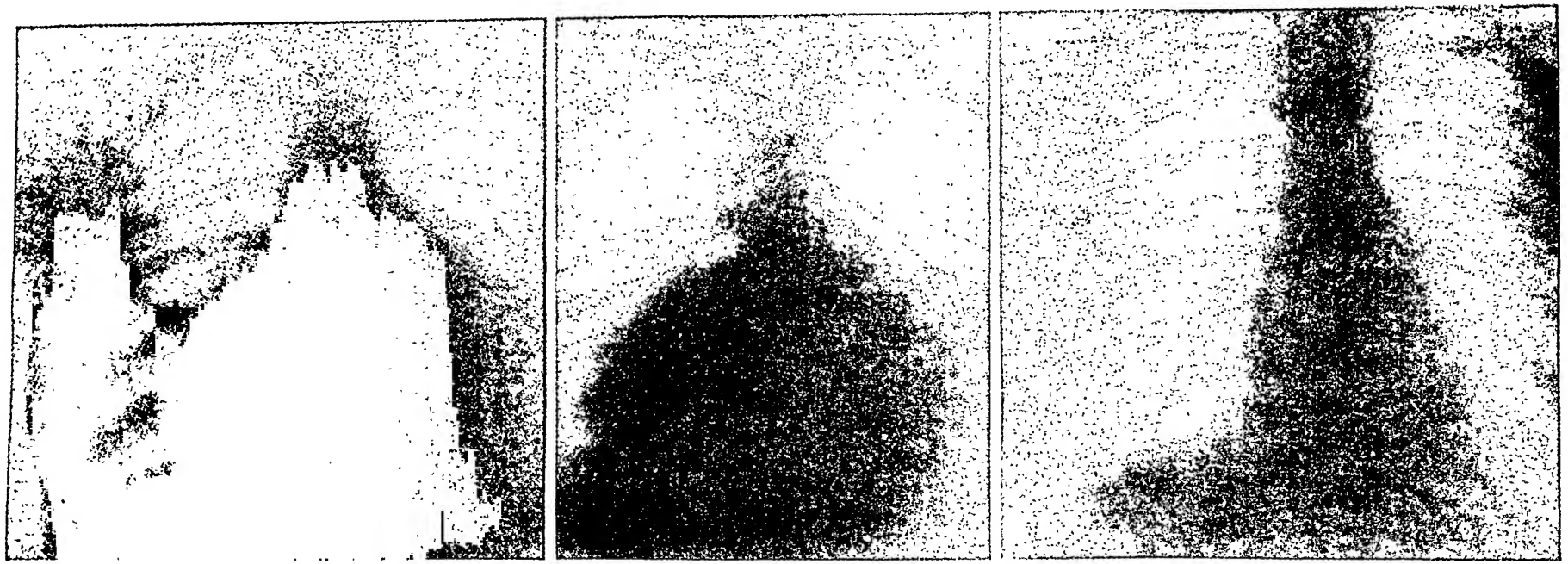
Treatment. As with pleural effusions the general constitutional aspect of the case is important. Once the diagnosis has been made in hospital the aim should be a careful sanatorium regime with its strict routine and discipline. From the point of view of local treatment mercurial diuresis may be considered, particularly in polyserositis, while pericardial paracentesis should be repeated where there is a massive effusion. The value of taking the venous pressure and doing an air replacement (pneumopericardium), even if only to determine the size of the heart and the thickness of the pericardium, should be appreciated. Where Beck's triad with chronic cardiac compression originated from a pericardial effusion or a polyserositis (provided that the tuberculous process is reasonably quiescent) surgery, in the form of pericardial resection, should be given serious consideration in view of some of the brilliant results that have been reported (Paul White 1935, Holmes Sellors 1944).

The following case reports will serve as an illustration of some of the points already mentioned.

Case Notes

Case 1.

A factory worker, aged 22, seen in January 1944, gave the following history: three weeks before Christmas she had an attack of "influenza" when she complained of headaches, giddiness, nausea, and tiredness in the legs. These symptoms lasted two days, and a week later she noticed slight swelling of the ankles and dyspnœa. She had no chest pain, palpitation, nor appreciable loss of weight.



A B C

FIG. 1.—Case 1. (A) X-ray of the heart, showing characteristic cardiac silhouette of a pericardial effusion.
(B) The same case following pericardial paracentesis and replacement of fluid by a small quantity of air (pneumopericardium). The comparatively thin pericardial wall is well shown.
(C) The cardiac silhouette is seen, three months later, practically returned to within the limits of the normal.

The past history included measles at the age of four, whooping cough at five, and scarlet fever at seven; there was no history of chorea or rheumatic fever and no family history of tuberculosis. On admission to Leatherhead Emergency Hospital she was obviously ill, pale, and toxic. There was slight cyanosis of the lips, some dyspnœa, and some engorgement of the neck veins, but the girl was able to lie flat. Temperature range 97–100; pulse regular and 120; respirations 24. Mantoux test, 1 in 1000, was positive.

Examination of the heart. Apex beat not palpable; heart greatly enlarged to right and left; area of cardiac dullness 8 cm. to right of sternum and 17 cm. to left; heart sounds faint; rhythm regular; blood pressure 135/100 ; no murmurs heard; no friction audible; signs of compression at the left base.

Fig. 1A shows gross enlargement of the cardiac silhouette, characteristic of a pericardial effusion.

A cardiogram showed low voltage curves and flat T waves in all leads, quite in keeping with pericardial effusion. The T waves were improved in a subsequent cardiogram.

Blood count: red cells 6·5 million; hæmoglobin 56 per cent; colour index 0·4; white blood cells 8500; nothing abnormal in differential count.

Pericardial paracentesis yielded 600 c.c. of clear, straw-coloured fluid which clotted readily on standing: S.G. 1030; total protein 4·7 g. per 100 c.c.; albumin 3·9; globulin 0·8; culture sterile. A pneumopericardium was attempted but she felt faint after 100 c.c. of air had been introduced and it was discontinued (Fig. 1B).

Guinea-pig inoculation: animal killed two months later, no evidence of tuberculosis.

Repeated pericardial paracentesis, performed at intervals, yielded only small quantities of serosanguinous fluid; blood sedimentation rate was 10.

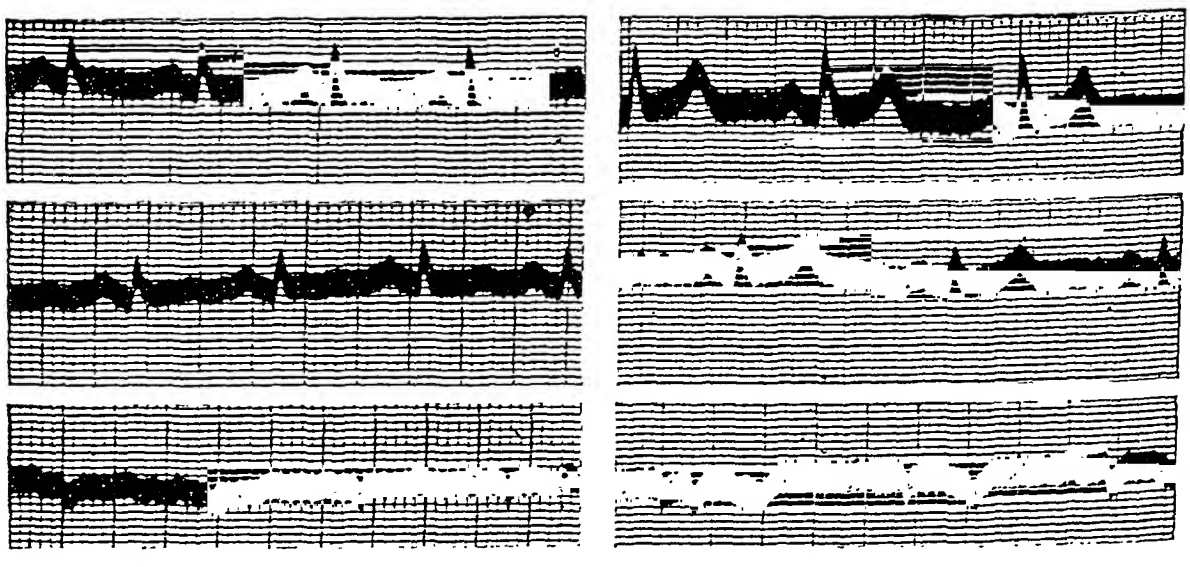
Two weeks later the cardiac dullness had become greatly reduced but pericardial friction now heard to the left of the sternum. In the third month her condition had improved enormously: her pulse rate became normal. An X-ray showed a cardiac silhouette approaching the normal (Fig. 1C). The cardiogram showed better formation of waves T I and T II. On discharge hæmoglobin was 98 per cent.

Seen at regular intervals since her discharge, during which time she has followed a careful sanatorium regime, this girl has no clinical or X-ray evidence of cardiac abnormality and is back at work. I have little doubt that her condition was due to a tuberculous pericardial effusion.

Case 2.

A married woman, aged 34, admitted to the Leatherhead Emergency Hospital complaining of substernal tightness and pain, palpitation, lassitude, loss of weight, and slight breathlessness of three months' duration.

Her previous history was a good one with no evidence of rheumatism. Her mother had died of pulmonary tuberculosis.



A B

FIG. 2.—Case 2. (A) Electrocardiogram before treatment: showing low voltage deflections and slight left axis deviation. (B) After treatment: R is now higher voltage and T I and T II are considerably improved.

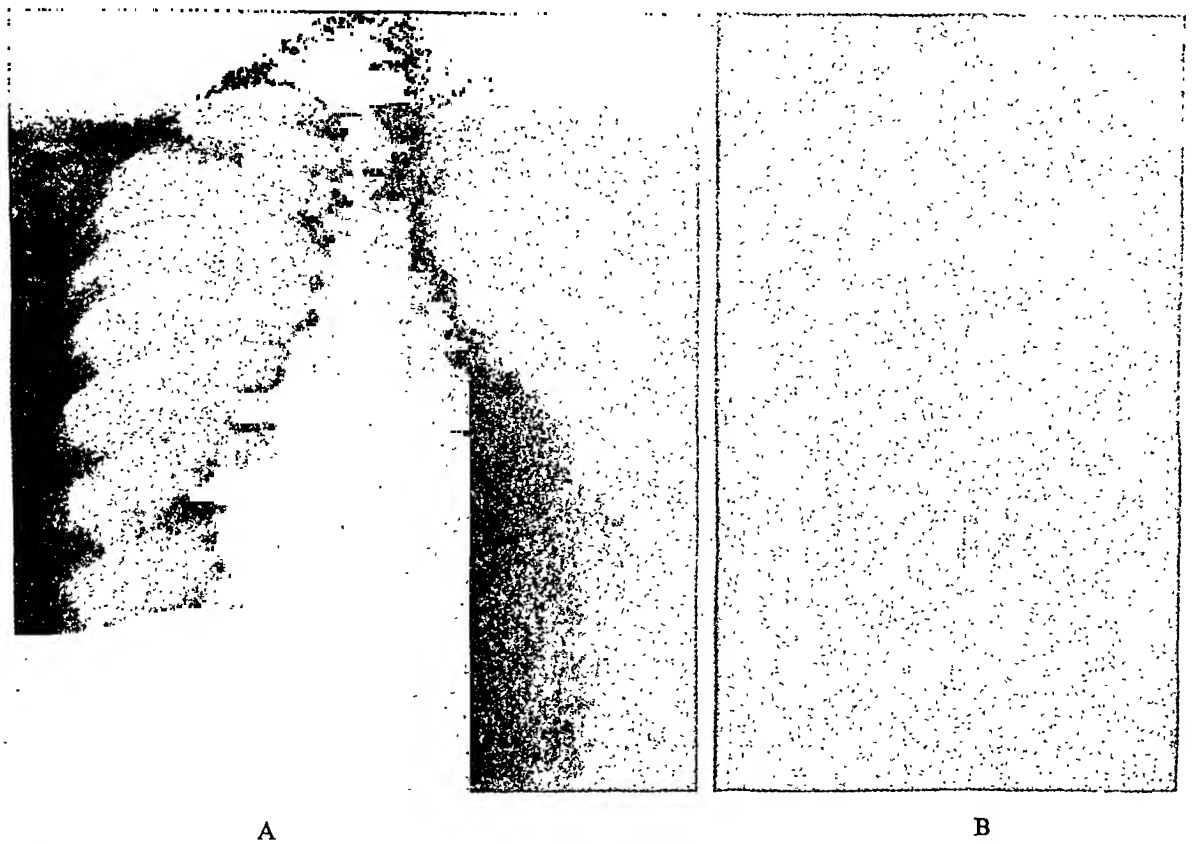
She was not cyanosed; temperature intermittent (97–99·4); pulse 90 and regular; respirations averaged 24; no engorgement of neck veins; blood sedimentation rate 39 ; blood count normal.

Examination of the heart. Apex beat in normal position, but an increased area of cardiac dullness to left and right; no murmurs; pericardial friction heard at base; B.P. 120/90. X-ray examination confirmed the clinical diagnosis of pericardial effusion.

A cardiogram showed small low voltage deflections and flat T waves in lead I. Following treatment subsequent records showed higher voltage curves and improvement in T waves (Fig. 2A and B).

Pericardial paracentesis on two occasions yielded a blood-stained effusion which, on examination, showed a moderate number of leucocytes (82 per cent lymphocytes); total protein 5·8 g. per 100 c.c.; direct smear showed no organisms; culture sterile; guinea-pig inoculation negative after three months.

This case is regarded as a case of tuberculous pericardial effusion in spite of the negative guinea-pig test. Serial clinical, radiological (Fig. 3A and B), and cardiographic examinations have, since her dis-



A B

FIG. 3.—Case 2. (A) Characteristic cardiac silhouette of a pericardial effusion. (B) Showing cardiac silhouette almost within the limits of the normal, following pericardial paracentesis.

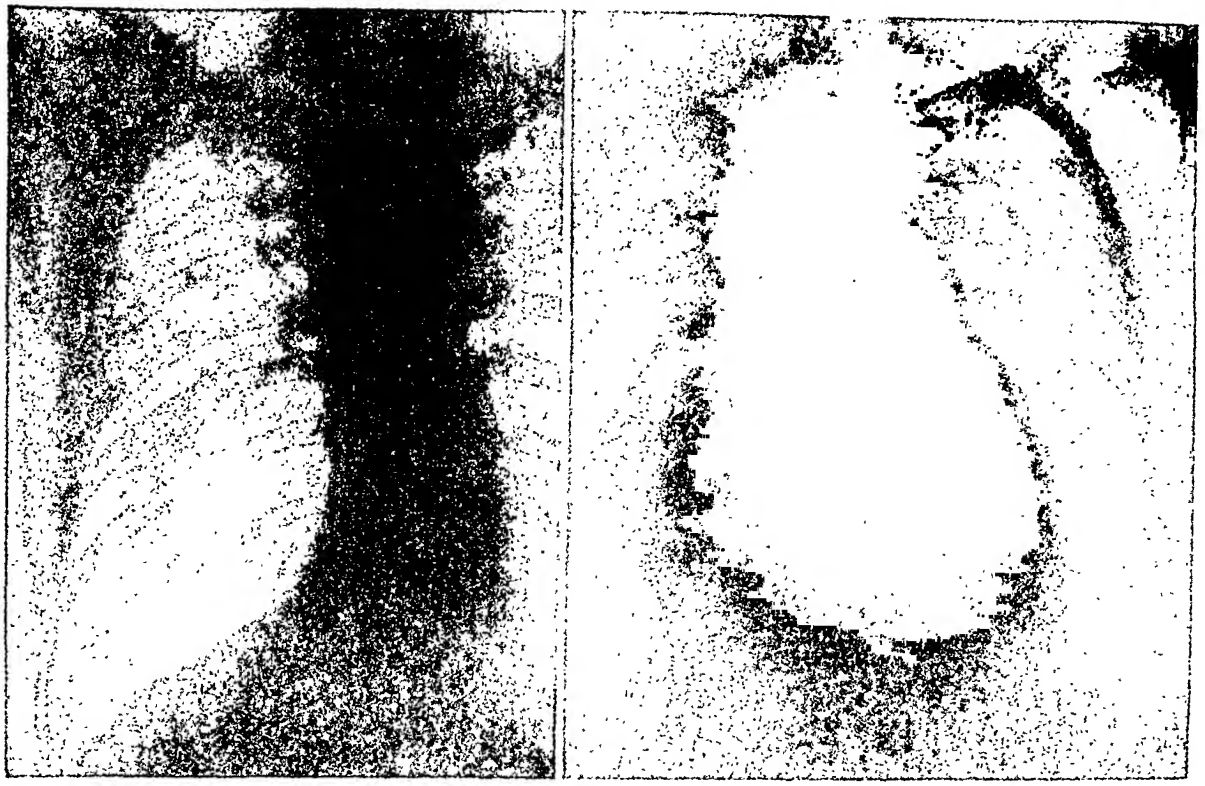
charge nearly three years ago, shown progressive improvement. She now has no symptoms nor any cardiac abnormality.

Case 3.

A labourer, aged 52, had extensive bilateral pulmonary tuberculosis and tubercle bacilli were present in large numbers in the sputum. He was in a sanatorium for six months in 1942, where he made satisfactory progress and gained 1 stone in weight, but the sputum remained bacilliferous. There was then no evidence of any cardiac disease (Fig. 4A).

When seen again a year later he was much worse, was cyanosed, and had a cough with much sputum. Temperature 101; pulse 130; and clinical examination showed obvious re-activation of the disease in both lungs. It was, however, with the greatest astonishment that I discovered on the routine skiagram, in addition to the extensive lung infiltration with cavitation, a cardiac silhouette highly suggestive of a pericardial effusion (Fig. 4B). The patient died in the sanatorium four days later.

Post-mortem examination (confined to the chest). Both pleuræ obliterated by fibrous adhesions; massive caseous glands in both hilar regions. Lungs showed extensive fibrocavernous disease. Pericardial cavity appeared to occupy nearly two-thirds of the thoracic cavity and contained a thick, blood-stained, loculated effusion.



A B

FIG. 4.—Case 3. (A) X-ray of the chest, showing extensive lung infiltration with cavitation, involving upper and middle zones of both lungs. (B) The same case twelve months later, showing extensive lung infiltration with cavitation complicated by a massive pericardial effusion.

FIG. 5.—Case 3. Photograph of the heart and pericardium. The thickened pericardium is well seen, with the characteristic exudate on the surface of the heart and pericardium (bread and butter pericardium).

Dr. J. N. Cummings, who examined the heart and pericardium very completely, also kindly photographed it for me and took sections of the pericardium of which he has been good enough to supply me with microphotographs. He reports as follows on the heart, pericardium, and pericardial fluid.

The heart was considerably enlarged, measuring 14·5 × 10·7 cm. after removal of pericardial sac.

Left ventricle hypertrophied, thickness of left ventricle wall being just under 2·5 cm. from apex. Muscle covered all over by a thick visceral pericardium which varied from 0·5 to 1 cm. and was composed of a granular pink- or grey-coloured granulation tissue. Parietal pericardium grossly thickened, being 0·5 to 1 cm. in thickness and consisting (naked eye) of fibrous tissue and granulation tissue with considerable irregularity of surface. On the irregular surface of the parietal pericardium in the fixed specimen were considerable collections of rather gelatinous material, some up to 1 cm. in thickness (Fig. 5).

Histological examination. Sections were cut of the pericardium, and also of the heart muscle. No tuberculous lesions were found in the heart muscle itself. The section of the pericardium showed a fibrinous exudate lying upon typical tuberculous granulation tissue. Giant cells and tubercle formation could be found with ease. There was a fair amount of mononuclear cellular infiltration throughout. Tubercle bacilli found in some numbers in the section (Fig. 6).

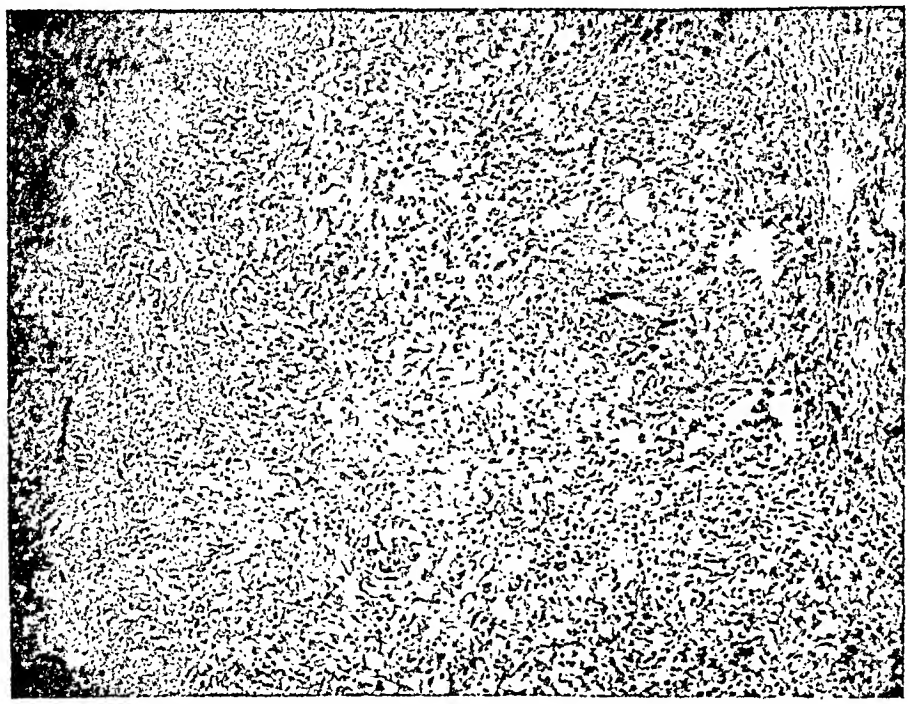


FIG. 6.—Case 3. Microphotograph of the pericardium, showing typical tuberculous granulation tissue and giant cell formation. Magnification × 50.

Pericardial fluid: blood-stained; red blood cells 47,000 per cub. mm.; white cells 900 per cub. mm.; polymorphs 10 per cent; lymphocytes 90 per cent; protein 3·0 per cent; specific gravity 1040; direct smears, a very few tubercle bacilli present; cultures, a fair growth in two weeks.

Case 4.

A gardener, aged 20, had an acute attack of " influenza " in February 1941, after which he complained of increasingly severe breathlessness, a cough with a trace of mucoid sputum, and some swelling of the legs. His previous history showed no noteworthy illness, nor was there anything relevant in the family history.

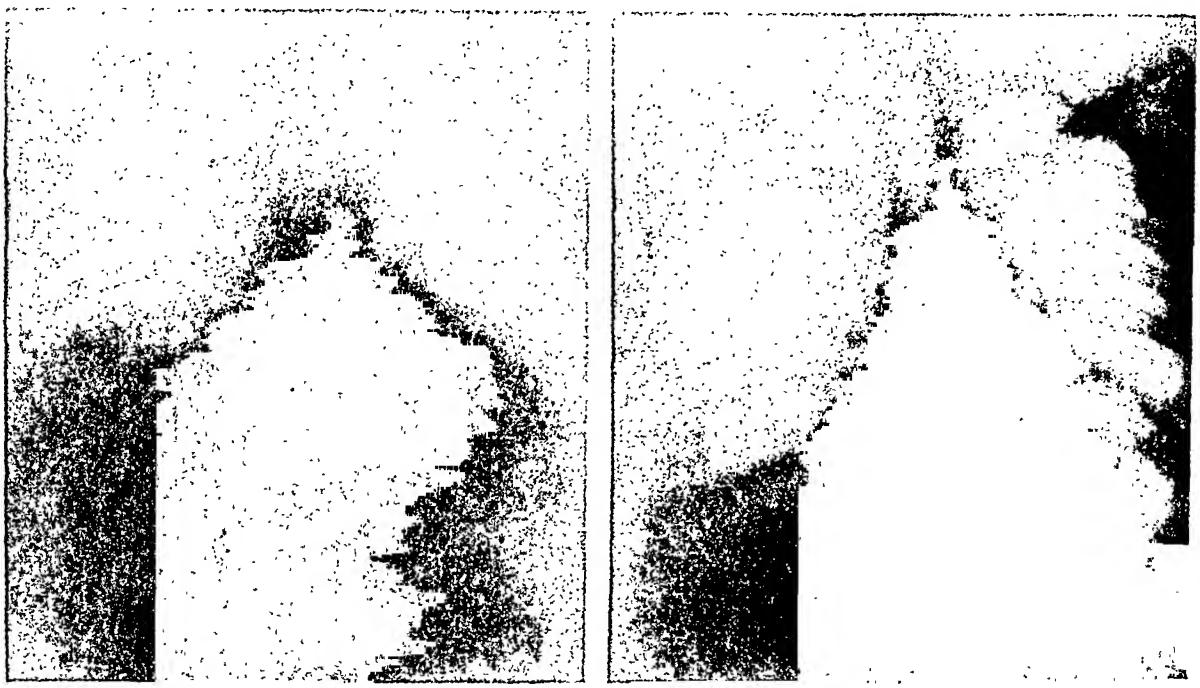
Admitted to hospital seven weeks after onset of illness, very ill and grossly orthopnœic; temperature range 97 to 102·8; pulse 130; no appreciable chest pain; no cyanosis or engorgement of the veins of the neck.

Examination. The chest showed marked limitation of movement on both sides, but especially the left; bulging of the præcordium; marked dullness over the left side up to the second intercostal space; breath sounds absent over areas of dullness.

Heart: apex beat not then palpable; heart sounds distant and feeble; rhythm regular; rate 130; B.P. 130/75; no significant murmurs, but for three weeks after admission pericardial friction heard at base of heart.

Abdomen: ascites; liver palpable; some œdema of legs; urinary output at first diminished but became normal.

X-ray examination of chest showed a bilateral pleural effusion, particularly marked on left. After aspiration of left-sided effusion cardiac silhouette markedly increased and strongly suggestive of pericardial effusion (Fig. 7A).



A B

FIG. 7.—Case 4. (A) The left pleural effusion has been aspirated; the right pleural effusion and the pericardial effusion are well seen. (B) Following pericardial paracentesis and replacement by air: the size of the heart and the thick pericardium are well seen.

Electrocardiogram showed rather low voltage curves in limb leads; T waves in all leads negative, especially præcordial.

All these findings were highly indicative of an acute polyserositis, including a big pericardial effusion, which was confirmed by paracentesis of pleuræ and later of pericardium.

Biochemical and pathological investigations: 21/4/41.

Pleural fluid: clear, straw-coloured, some clotting; polymorphs 2 per cent; lymphocytes 98 per cent; culture sterile; Ziehl-Neelsen, no tubercle bacilli seen; total protein 4·65 mg. per 100 c.c.; serum albumin 2·06; serum globulin 2·59; albumin globulin ratio 0·79.

Pericardial fluid: clear, straw-coloured fluid; polymorphs 90 per cent; lymphocytes 10 per cent; culture sterile; Ziehl-Neelsen, no tubercle bacilli seen; total protein 4·7 mg. per 100 c.c.; serum albumin 1·75; serum globulin 2·95; albumin globulin ratio 0·59.

The differences between the cytology of the pleural and pericardial fluids are noteworthy.

Guinea-pig inoculation with pleural and pericardial fluids both showed tubercle in spleen and lungs.

Urine: albumin, a trace; deposit; an occasional red and white blood cell seen; direct smear, no organisms seen; culture, no growth.

Blood: B.S.R., 34 mm. at end of one hour; hæmoglobin, 78 per cent.

Treatment and progress.

The patient was treated on general lines for his tuberculosis and paracentesis of pleuræ and pericardium were performed. The fluid in the pericardium was replaced by air on several occasions and there was clinical evidence of a hydro-pneumopericardium with characteristic auscultatory physical signs of a " tinkling splash " over the præcordium. He also had a course of salyrgan.

An X-ray film in January 1942 (Fig. 7B) showed a pure pneumopericardium with no fluid and a corresponding disappearance of auscultatory signs. The thickened pericardium was well seen radiologically and the heart did not appear enlarged. Ascites and œdema of the legs had completely subsided. There was a small right pleural effusion, but the left one had resolved completely. He was afebrile and the pulse was 80–100.

His general condition was good: increase of weight; normal blood sedimentation rate and blood count; and repeated examinations of the pleural fluid showed no change in cytology. Examination of pericardial fluid now showed 88 leucocytes per c.mm., now mainly lymphocytic.

The interesting features of the case at this stage were focused on the relatively good, temporary, response to treatment; the original difference in the cytology of the pleural and pericardial effusions; and the question whether the introduction of a pneumopericardium could have any influence in the prevention of chronic adhesive pericarditis (Pick's disease).

The patient spent twelve months in a sanatorium during 1943 and returned to the Leatherhead Hospital in 1944. His progress had been well maintained, but by April he was beginning to develop some engorgement of the neck veins and suggestive evidence of incipient constrictive pericarditis, confirmed by the development of a generalized anasarca with gross œdema of the legs, sacral œdema, ascites, and liver enlargement. He also had a high venous pressure and the circulation time (solution of saccharine, arm to tongue) was 28 seconds.

The possibility of a pericardial resection was under consideration, but in June, owing to the war situation, we were obliged to evacuate civilian patients to the North, where treatment was continued on the lines outlined, pericardial puncture yielding no fluid. He died suddenly in February 1945, and, most unfortunately, permission for post-mortem examination was not obtained. The case appears to have ended in a Pick's disease, secondary to a polyserositis.

Case 5.

A clerk, aged 31, came into Leatherhead Hospital complaining of breathlessness and swelling of the legs and feet. His disability dated back to a cold in 1939, followed by pneumonia, after which

FIG. 8.—Case 5. Characteristic cardiac silhouette of a pericardial effusion with a right pleural effusion: pear-shaped, in the erect position: compare Fig. 9.

he developed a right-sided pleural effusion with the symptoms mentioned. During convalescence the dyspnœa was a constant feature while the œdema was transient. Despite this he had been able to continue with his clerical job. He complained of pain in the form of a " tight constriction " below the ribs on exertion.

On admission he was dyspnœic, even at rest, and had a dry cough causing extreme breathlessness; he was plethoric and generally cyanosed, especially the arms and extremities; no clubbing of the fingers; no history of any acute rheumatism, but a suspicious family history of tuberculosis.

Examination. Neck veins engorged; heart grossly enlarged; apex beat palpable in fifth space, just outside normal limits; increased dullness to right and left; B.P. 120/90; trachea centrally placed; no significant murmurs.

X-ray examination. Cardiac silhouette, gross enlargement to right and left, highly suggestive of a pericardial effusion, pear-shaped in erect position (Fig. 8), but more rectangular in recumbent position (Fig. 9). A noteworthy feature, and of some diagnostic significance, was the marked

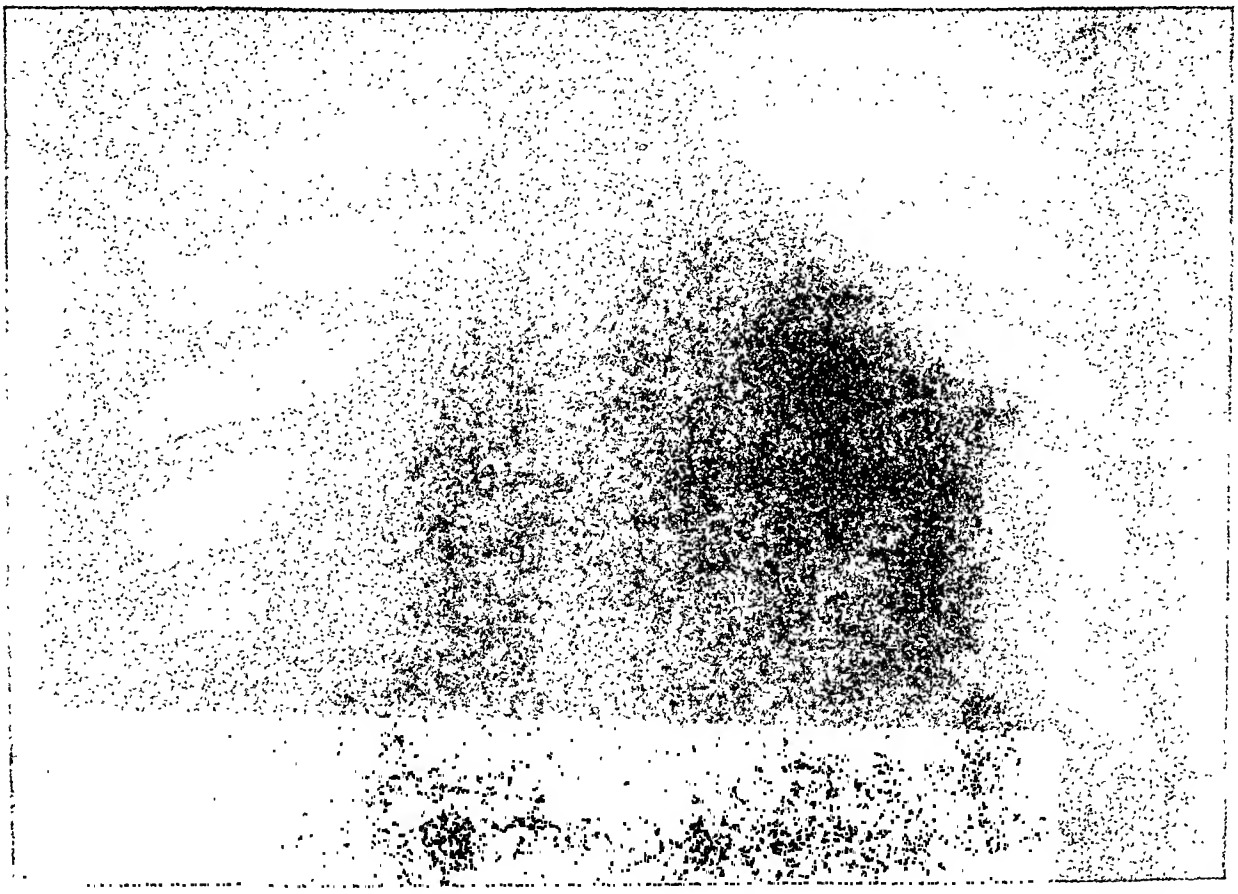


FIG. 9.—Case 5. The same patient recumbent, showing a cardiac silhouette more rectangular in shape.

calcification of the superior tracheo-bronchial glands, specially well seen in the lateral and right anterior oblique positions. Radioscopy showed almost complete absence of pulsation in the lower two-thirds of the right and left borders, but the upper third appeared to pulsate normally.

There was a right-sided pleural effusion which on puncture was straw-coloured, clotted readily on standing, revealed no organisms; sterile on culture; fluid mainly lymphocytic; protein content 4 per cent; blood count showed an erythrocytosis; blood sedimentation rate normal; pericardial puncture yielded no fluid but feel of needle gave impression of an obviously thickened pericardium with, possibly, a loculated or encapsulated effusion. Venous pressure 18 cm. (sodium citrate); circulation time (arm to mouth) 37 seconds (normal 16). Electrocardiogram not pathological.

Liver palpable, 10 cm. below the subcostal margin; gross œdema of legs.

My impression of this case has been that there has been a polyserositis, almost certainly of tuberculous origin—the calcified mediastinal glands seen radiologically give strong confirmatory evidence of this view—and he is now developing a constrictive pericarditis with gross thickening of the pericardium. Fluid may be present, in which case it is either loculated or is so thick that it cannot be aspirated through an ordinary needle. Gross cardiac enlargement (certainly not due to rheumatic

heart disease), complete absence of cardiac murmurs, absence of a rheumatic history, low blood and pulse pressure, absence of cardiac pulsation on radioscopy, high venous pressure and prolonged circulation time, all strongly favour the diagnosis. In view of the problem in diagnosis Dr. Terence East kindly saw this case with me and agreed that, despite the normal cardiogram, the various findings strongly favoured this diagnosis. The patient was to see a thoracic surgeon with a view to a pericardial resection. Unfortunately he is schizophrenic and his confused mental state will not permit this for the present.

Case 6 (*Dr. John Parkinson*).

Whilst discussing the subject of tuberculous pericarditis with Dr. John Parkinson he brought to my notice a case he had under his care during the last war which presents a number of features of such interest that he has very kindly permitted me to quote extracts from it.

The patient, aged 22, was admitted to hospital at Rouen in 1917, ten days after complaining of a "cold", with weakness, cough, and loss of appetite. Previous history was good with no acute rheumatism, chorea, or tonsillitis.

Examination. A fairly well-nourished youth; whole face slightly puffy and glossy, eyelids not more than the rest; cheeks highly coloured, showing, with the lips, a degree of cyanosis. He could lie quite flat in bed but even when supported by two pillows there was slight objective dyspnœa. Only complaints were occasional cough and slight præcordial pain; temperature on admission 100; respirations 34; radial pulse very small, rate being approximately 130 and very irregular.

Examination of the heart showed no præcordial pulsation; area of deep cardiac dullness greatly increased, especially to left where it reached anterior axillary line; second left intercostal space dull to percussion; no abnormal dullness to right. On auscultation: no pericardial rub; heart sounds distant and unaccompanied by murmurs; dullness at base of left lung and in infra-axillary region, with crepitations and diminished breath sounds; bronchial breathing not heard. No abnormal signs discovered in abdomen and no pitting of legs on pressure.

Urine: examined three times, on each occasion a cloud of albumin present on boiling, but no casts found.

Radiographic examination showed pericardial sac greatly distended with fluid and a free left pleura.

Puncture of pericardium: performed five days after admission; 150 c.c. fluid aspirated (clear, except for a few small flakes), the needle showing the movements of the heart as it beat against it. Fluid sterile on culture, despite subsequent positive findings of tuberculosis. Aspiration produced little or no improvement; a course of sodium salicylate likewise unsuccessful.

For two months little change occurred. The patient ate and slept well; temperature irregularly remittent, at time intermittent, reaching 100 to 103 each evening; pulse 120–140 with extra systoles.

The pericardium was punctured on two further occasions; on the first 375 c.c. of clear fluid were removed; on the second 150 c.c. of slightly turbid fluid, but on both occasions it was sterile. During the last two months of his life there was moderate œdema of loins and legs. During the third month of the illness the general condition became worse. The sputum, previously scanty, now became profuse and purulent. When examined a fortnight before death it was found to contain tubercle bacilli. Apart from the signs at the left base nothing abnormal was found on examination of the lungs until the middle of April, when a few rhonchi were heard generally. By this time the patient was mentally dull during the day and mildly delirious at night. He became unconscious and died in May.

Post-mortem examination. This showed, briefly, a pericardial cavity occupying two-thirds of the space of the left pleural cavity and containing 2000 c.c. of dark straw-coloured fluid. The walls of the pericardial cavity were thickened, at some points to the extent of 0·5 cm.; the surface of the heart was covered with thick fibrinous exudate (bread and butter pericardium). The heart was of moderate size with no valvular lesions, and the lung substance showed, fundamentally, miliary tuberculosis.

Summary and Conclusions

Tuberculous pericardial effusions, usually secondary to mediastinal gland tuberculosis, are probably not as uncommon as we have been led to believe. The condition may occur at all ages, and is not necessarily associated with gross symptomatology.

The combination of clinical, radiological, and cardiographic examinations and pathological investigations of the pericardial fluid are of great value in the diagnosis of the disease in the living subject.

Pericardial paracentesis in a suspected case is always advisable for diagnostic purposes and

carries with it no undue risk. A characteristic straw-coloured lymphocytic exudate, as with a pleural effusion, should, despite negative findings for tubercle bacilli and guinea-pig inoculation, arouse very real suspicion of a tuberculous ætiology.

The induction of a pneumopericardium may have some therapeutic value, apart from its diagnostic value in assessing the size of the heart and the degree of thickening of the pericardium.

The relationship of a tuberculous pericardial effusion and polyserositis to a developing constrictive pericarditis (whose ætiology is probably tuberculous) is noted, and the great value of surgery in the quiescent stage of the latter must be appreciated.

The prognosis of tuberculous pericardial effusions, whilst dependent upon the nature of the fluid and the accompanying complications, is not necessarily associated with a high mortality rate. A fluid negative both on culture and to guinea-pig inoculation may occur and yet other diagnostic criteria may point to a tuberculous ætiology. In such cases the prognosis would appear to be correspondingly more favourable.

I am indebted to Dr. Terence East for the electrocardiograms of all my cases; to Dr. David Nabarro and Dr. John Dacie for pathological investigations; to Dr. C. Gray for biochemical investigations and to Dr. J. N. Cummings for photographs of Fig. 5 and 6.

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MERCURIAL DIURETICS

INTOLERANCE AS SHOWN BY SKIN SENSITIVITY

BY

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The rarity of adverse effects following the use of mercurial diuretics is remarkable, considering how widely they are now employed. Many regular recipients with heart failure and, less frequently, with renal œdema would at least be confined to their beds but for these preparations. The causes of the few complications reported have been uncertain and idiosyncrasy or allergy has often been given as an explanation. Having seen many cases who receive doses of this drug with impunity for years, the temptation is to dismiss the explanation of simple accumulation. A hitch in a standard regime, however slight, is often interpreted as a contra-indication of the further use of a drug, although the cause of the untoward effect is not known. Such an abandonment in the case of mercurial diuretics frequently leads to a deterioration of the patient's health, and a fuller understanding of such reactions is therefore important.

Wolf (1931) reported a case of sudden death following intravenous salyrgan in a child aged four, with nephrosis; the injection preceding the fatal one caused a chill, fever, a morbiliform rash, and anorexia; but resulted in satisfactory diuresis although previously the output had been disappointing. Keith (1936) stated that injections of organic mercury might be followed by stomatitis, diffuse dermatitis, diarrhœa, hæmaturia, and renal insufficiency, but considered that these reactions were rare. He also noted that if the mercurial diuretics were discontinued for about ten days the drug could often be given again with satisfactory results. Klein and Seymour (1942) discussed several cases with skin reactions. In one, urticaria appeared after eight consecutive injections at unstated intervals, and an evanescent erythema followed the final two injections in this case. A transient erythema was seen in others, one of which after further salyrgan injections developed an " inflammatory reaction of the skin which progressed to a typical exfoliative dermatitis." In their opinion these cutaneous manifestations were warnings of more serious reactions to follow, and contra-indicated further use of the drug. A discussion of cutaneous eruptions produced by mercurial diuretics with many references is to be found under the names of De Graff and Nadler (1942). Types of reactions so produced include urticaria, small reddish spots or purpuric areas, and morbiliform or scarlatinaform erythemata; occasionally the rash was followed by desquamation in one to three weeks. They suggested that positive patch tests indicated an allergic basis and that although an accumulation was seen with the older type of mercurial diuretic, it did not occur with the rapidly excreted theophylline-containing mercurials. They also pointed out that an erythematous skin eruption may follow either the first or any subsequent injection of the diuretic. Relationship to dosage or excretive response was, however, not considered. Other theories have been suggested. According to Lesser (1888) peripheral vasodilatation is caused by the paralysing effect of mercury on the sympathetic nerves. The histological studies of Almkvist (1922) also indicate the cutaneous capillary dilatation is caused by mercury. Their studies of the reactions produced by mercurial diuretics in a woman, aged 27, with rheumatic heart disease were reported by Fox, Gold, and Leon (1942). Several mercurial preparations were found to affect her similarly and their experiments showed that the xanthine content of these substances was not to blame.

Engel (1937) quoted by Barber (1938) stated that novurit suppositories " should not be given at an interval of less than five days. Adherence to this rule renders the patient tolerant

of repetitive suppositories over a period of years without the production of a chronic inflammatory reaction in the rectal mucosa." This statement suggests that frequent application of the mercurial may lead to sensitization. Barber considers that signs of mercurial poisoning are "a sequel to failure of elimination when, as sometimes happens, diuresis does not occur." The effects which manifest themselves include stomatitis, diarrhœa, vomiting, hæmaturia, and purpura. Evans and Perry (1943) mention skin rashes caused by mercurial diuretics but do not associate them as forerunners of more serious things. Other authors have commented on the freedom of this treatment from serious complications (Evans and Paxon, 1941). We report the following new cases of skin erythema following the administration of mercurial diuretics.

Case Reports

Case 1. A trolley bus conductor, aged 48, had essential hypertension with heart failure. Dyspnœa on exertion and nocturnal asthma started in 1942, and œdema of the legs in November 1943; from that time onwards he received from his private doctor 2 c.c. of neptal intravenously, three times a week with a good but diminishing diuretic response. In February 1944 a faint generalized pink rash with irritation was noticed, which steadily increased with each injection. He was then referred to one of us (A.B.). A positive patch test to neptal confirmed the suspicion that the rash was caused by that drug. A control test on a student was negative. The use of neptal was accordingly discontinued and the rash gradually faded. The patient's symptoms of cardiac failure, however, soon returned. By June, nocturnal dyspnœa was severe and so neptal was given again in doses of 2 c.c. twice a week. No recurrence of the rash or irritation took place. From July 1944 until his death in December, he was under our observation. Apart from a weakly positive result in August, patch tests frequently repeated, proved negative, as did similar tests to other organic mercurials including mersalyl, esidrone, and salyrgan. Although severe failure rendered necessary the use of frequent mercurials, neptal 2 c.c. every third or fourth day, and rest in hospital, the original dosage of 6 c.c. in a week was not employed from February 1944 onwards, and the diuretic response was excellent varying from three to four pints. It would appear that this man could tolerate 4 c.c. of neptal weekly as long as his elimination was satisfactory, but that 6 c.c. in a week over a period of 3 months with less efficient diuresis led to accumulation and skin manifestations. After a rest of three months, but without any active densensitization he showed no reactions to further injections and only a faintly positive patch test on one occasion.

Case 2. A woman, aged 39, was first admitted to hospital with nephritis (Type II, Ellis, 1942) in January 1943. Œdema of the nephrotic type was gross. The blood pressure was 180/100. There was no heart failure. The urine was loaded with albumin. The blood area was normal, and the plasma protein 4·6 mg. per 100 c.c. Rest, limitation of fluids, and a high protein diet did not alter the plasma protein and the œdema remained. Neptal, 2 c.c. intramuscularly was therefore started on February 22, 1944 and given every fourth day preceded by 30 grains of ammonium chloride by mouth. The diuretic response was disappointing and seldom exceeded 50 oz. This dosage was continued until May 1943 when the œdema of her legs which had persisted, increased greatly. She was therefore rested once more as an inpatient and the effect of 3 c.c. neptal intramuscularly was observed. At four daily intervals three such injections did not meet with proportionate outflow, and so the dosage was returned to 2 c.c. twice weekly, while she attended as an outpatient. Readmission was again necessary in October 1943. Her œdema was worse and her plasma protein still low (4 mg.). The hæmoglobin was 104 per cent. Within two months she had lost one stone in weight. Before her discharge on December 24, 1943 the dose of neptal was increased to 2·5 c.c. twice weekly with improved but only moderate response. This dosage was continued from outpatients until February 26, 1944 when an injection was followed by a generalized itching with erythema, mainly of the upper limbs and thighs. On March 6, mersalyl 2 c.c. was substituted, but this again produced itching and enhanced the rash. Mercurial dermatitis being suspected, a patch test of neptal (full strength) with saline control was carried out and this was positive when observed after 48 hours. The diffuse rash was now dry, fine, scaling, and less pink. After mercurials had been discontinued for two months, a further patch test was found to be negative. Salyrgan 2 c.c. was tried on May 4, this only produced an output of 2 pints but there was no skin reaction. She returned to neptal 2 c.c. twice weekly but the injection on May 13 was followed four hours later by a return of the itching rash, which spread up to the arms from the wrists. Within the next 48 hours a slight recurrence was also noticed on the neck and thighs. The rash was red to pale pink, punctate, macular, and sometimes confluent. Dry scaling patches up to 0·5 cm. diameter in both anticubital fossæ dated from the previous rash was much more severe. Her output to the last injection produced 60, 56, and 38 oz. on consecutive days, during a daily intake of 30 oz.

Three days after that injection her blood count showed an eosinophilia of 5 per cent which might have indicated an allergic reaction. A patch test that same day was uncertain, as some redness was caused even by the control owing to the irritable state of her skin. Ten days after that injection, the rash was coarser, and more powdery, involving upper limbs, buttocks, thighs, and neck. Itching was still intense. By June 6, the rash had spread down to the legs although improvement was apparent

elsewhere. The most severe areas, the inner side of the forearms, then received 100 r unscreened X-rays with marked benefit, and this was followed one week later by similar dosage to the outer aspect of the arms. By July 4 the rash had nearly gone; patch tests to 25 per cent solutions of neptal, mersalyl, salyrgan, and esidrone with saline control were applied and these were all still negative after three days. Full strength patches of these mercurials applied on July 17 were also negative. Her skin had therefore become negative to patch testing in just over two months from the last injection of neptal, although no desensitizing doses had been employed. From July 18 at weekly intervals other mercurial diuretics were injected including esidrone 1 c.c., mersalyl 2 c.c., and salyrgan 2 c.c., and no skin reaction occurred. Finally neptal was again used with satisfactory effect in 2 c.c. dosage at weekly intervals, from August to September when a patch test was again negative. An improvement occurred in her condition at this time. The œdema diminished rapidly, and no further mercurials have been required.

It would appear that this patient tolerated 2 c.c. neptal twice weekly for ten months without any adverse effect in spite of poor diuresis, but after eight weeks of 5 c.c. instead of 4 c.c. in each week, a rash appeared. After two months without injections, she could tolerate further mercurials for a time, and her patch test was negative. The second skin reaction took six weeks to clear completely, and by this time she was again patch test negative.

Case 3. A woman, aged 63, was first seen in June 1943 suffering from hypertensive heart failure and auricular fibrillation. The blood pressure was 210/130 and there was aortic valve disease. Besides digitalis and reduced fluid intake, her treatment included weekly intramuscular injections of 2 c.c. of neptal. Although the diuretic response was not satisfactory, improvement was maintained until eight months later when she complained of intense generalized itching of the skin with a weeping rash of the thighs and arms. Neptal was discontinued and her skin condition cleared. As the œdema returned, Guy's pill (powered squill, digitalis, calomel, gr. i) was given three times daily. After two weeks the patient noticed a recurrence of the rash on her left thigh and this spread rapidly to form a band about six inches wide almost encircling the limb. Soon the generalized itching returned, it was therefore decided that the Guy's pill, containing mercury to which she was apparently susceptible, must be discontinued in favour of tab. digitalis folia. The skin condition improved immediately, but the œdema increased. Three further doses of Guy's pill caused an exacerbation of the rash, which confirmed the observation that oral administration of the mercury was to be blamed.

Four months later the patient was again seen in consultation. Her ascites and œdema were gross, a patch test to neptal was negative. Mercurial diuretics were not again tried until late in November 1944 when 1 c.c. neptal resulted in a urinary output of 83 oz. Subsequent doses at long intervals were not followed by cutaneous complications.

Case 4. This man, aged 58, was first seen in consultation in April 1944. Ten years previously he had undergone subtotal thyroidectomy and now showed evidence of hypothyroidism. The history and cardiogram also suggested a cardiac infarction one year previously. The blood pressure, 115/105, which rose to 230/170 under observation, breathlessness, œdema of ankles, and pulmonary congestion provided evidence of heart failure. Commencing on April 19, 1944 he received 2 c.c. neptal intramuscularly twice a week for 3 weeks, then once a week until June 14, 1944 after which injections were given every fortnight. His urinary output was not recorded but, satisfactory at the start, it diminished latterly. On August 1 he developed a diffuse rash over his abdomen, thighs, and the outer aspects of the arm. Intense itching accompanied the rash which was worse a few days after the injection. A neptal patch test was positive when removed after three days, an irritating erythema underlying the gauze square. His wife who was acting as control showed a completely negative result. Neptal injections were then recommenced once a month with satisfactory diuresis and no return of the cutaneous complication.

Although the injections were infrequent compared with those received by some other cases, possibly accumulation of mercury occurred because the diuresis after each dose was insufficient to ensure elimination. The individual tendency of such a patient to sensitization, however, must be taken into consideration.

Case 5. A woman, aged 53, was admitted to hospital with mitral stenosis, auricular fibrillation, and chronic heart failure. One week later, as her improvement with rest, adequate digitalization, and reduced fluid intake was not satisfactory mercurial diuretics were started. The first injection, 2 c.c. neptal intramuscularly, produced a diuresis of 104 oz. and a diminishing but satisfactory output continued over the next few days. On the third day after the first injection, neptal was repeated, this time producing 122 oz. in the subsequent 24 hours, with marked clinical improvement. After a further five days a third dose only gave a response of 68 oz. and about 1½ hours after this she vomited and complained of generalized itching No rash was seen although a careful watch was kept. Owing to an oversight the mercurial diuretics were not discontinued, and three days later a fourth injection of 2 c.c. neptal caused a similar irritation without a rash. A patch test applied after a lapse of three days showed a faint erythema with pin head vesicles; a control of saline was negative, as well as a neptal patch applied to a patient not receiving mercurials.

As the third injection met with a fair response only, a longer interval might have been allowed to elapse before the next injection. Itching of the skin too should have been sufficient warning that accumulation of the drug and sensitization of the skin were occurring.

Case 6. A man, aged 21, was admitted with heart failure and auricular fibrillation from mitral stenosis and aortic incompetence with stenosis. As the liver reached the umbilicus and ascites was starting without much peripheral œdema, congestive cirrhosis of the liver was suspected. Neptal intramuscularly in 2 c.c. doses twice a week had met with satisfactory diuresis from three weeks until one day before admission, when the last injection by the private doctor had proved inefficient. After admission and four days after the last mercurial, the same dose was given intravenously after premedication with ammonium chloride, with good diuresis. The injection of October 12, 1944 gave a response of 6 pints; but on the 16th no diuresis resulted. The next day the patient was drowsy, incontinent, with generalized œdema including the face, but with no orthopnœa. A diffuse blotchy pale pink rash had developed on the anterior aspect of the trunk, but no mention of itching was made at that time by the patient, possibly because of his mental torpor. Twitching of muscles, a blood urea of 140 mg. and an increase in albumin with a strongly positive guaiacum reaction in the urine, told of acute nephritis which was attributed to the mercurial treatment. The blood pressure, previously varying from 140/50 to 150/70 rose to 200/100 on October 13, and fell to the previous level after four days. A neptal patch test on the arm was then negative as were scratch tests, but a second patch test applied on the 19th in the scapular region was positive.

Normal rhythm was regained on October 19 and the patient's general condition improved. On that date, however, three days after the unsuccessful injection, the rash was more pronounced, particularly on the abdomen. The face was less puffy, and cerebration was clearer, but the breath was fœtid owing to stomatitis. During the next week the rash gradually faded. The urinary output equalled the intake (30 oz.) and the albuminuria diminished. Subsequently the nephritic element improved rapidly, and from the 25th the urine was reported clear. Œdema was still gross in spite of improving output, and so on October 29 a patch test to neptal having been found negative, 1 c.c. was given intramuscularly. This met with an excellent response. The trunk was now almost clear of rash which, however, still remained in a maculo-papular form on the extremities. On November 3, 36 hours after a further intramuscular injection (2 c.c. neptal) a papulo-erythematous rash recurred over the extremities and trunk with great itching. A patch test again proved positive. Eight days later, another neptal injection was tried with entirely satisfactory results and no untoward effects. The rash was now fading but scaling. Œdema of the lumbar region was still gross. Subsequently the use of neptal was continued intramuscularly at weekly intervals, and patch tests were always negative before each injection. The diuretic response varied between 90 and 130 oz. Ascites required paracentesis although peripheral and pulmonary œdema was controlled satisfactorily considering the severe degree of cardiac failure. Recently a trial of Guy's pill, one thrice daily, was made without effect, and was discontinued after five days. At the end of this trial course 2 c.c. neptal produced a diuresis of 186 oz. and a patch test to neptal was negative.

The mercurial preparation not only showed the presence of sensitization in this case, but also produced stomatitis and probably an acute nephritic reaction. All these ill effects were overcome by reduced dosage and careful administration of the drug. Had neptal been abandoned, it is doubtful whether this patient would have left his bed; as it was, he led a quiet life as an out-patient until a sudden decline at the end of April 1945. All excess fluid was eliminated satisfactorily, except the ascites, caused by hepatic cirrhosis for which occasional tapping was required.

Case 7. A male, aged 47, was admitted under the care of Dr. Horace Evans in December 1941. He was a case of insidious nephritis (Type II, Ellis, 1942). A left nephrectomy had been performed in 1922 for renal tuberculosis. His renal efficiency tests showed slight impairment (blood urea 50 mg. per 100 c.c.) In January 1942 before his discharge he received one injection of neptal 2 c.c. intramuscularly with a response of 102 oz. (intake 48 oz.). He was under observation as an out-patient with a varying œdema of the ankles but received no further mercurial injections until January 1944. Two injections at an interval of one week were then followed by the administration of neptal tablets by mouth, the dose of which was 2 t.i.d. for two days in each week, after a preliminary trial of 1 t.i.d. on the first occasion. This dosage was continued until March 15 when it was noted that the tablets caused " a lot of acid " and retching. The intramuscular preparation was therefore recommenced instead of the tablets. Œdema was now increasing steadily. On April 5 the urinary output was 5 pints and his blood urea 48 mg. per 100 c.c. The diuretic response to neptal continued to be satisfactory, reaching 10 pints on May 13 and 4 pints on June 14. On July 26 an itching of the skin was treated by calamine lotion, but neptal continued in the previous dosage (2 c.c. weekly) until he was referred to one of us (A.B.) on September 6. There was a generalized symmetrical rash and œdema of his legs was slight, so it was recommended that mercurial diuretics should be omitted. On October 5 the rash was fading well, and patch tests which unfortunately had been previously omitted, were now negative both on the arms and at the site of the injection (buttock).

In spite of some degree of renal insufficiency, mercurials had been well tolerated from January until July 1944, although it is likely that renal impairment led to an accumulation of mercury over several months. The persistent œdema required the continuation of this regime, and, in the light of our experience since this investigation started, this patient would probably have continued to tolerate mercurial treatment had the interval between the doses been increased.

Case 8. A male, aged 54, was admitted with hypertensive heart failure on January 19, 1945 (B.P. 200/140). His urine was clear, and his blood urea was 58 mg. Œdema was extensive in the lumbar region and lower limbs. Cardiograms supported the diagnosis of hypertension without coronary obstruction.

His first neptal, 2 c.c. intramuscularly on January 25 was followed by a urinary output of 90 oz. Two days later a similar dose produced no diuresis, but output exceeded the fluid intake of 30 oz. by 12, 32, and 30 oz. on that and the subsequent two days. Two days after the second injection, he complained of generalized itching. His blood urea then was 62 mg. and his B.P. 160/90. As his œdema was increasing and a left pleural effusion had developed, neptal was given on January 31. Within three hours of this a morbiliform rash was noticed over his trunk and limbs. The urinary output that day only exceeded intake by a few ounces, and next day rectal incontinence disturbed the fluid measurement. No satisfactory diuresis resulted. A patch test applied 44 hours after the onset of the rash, was negative in 24 hours, but positive in 48 hours. The patient became worse and died on February 7. At autopsy there was no evidence of nephritis and signs of hypertensive heart failure were present.

Case 9. A retired clergyman, aged 83, was admitted to another hospital in August 1944 with coronary thrombosis. Three weeks later œdema slowly developed. From September 2, 1944, mersalyl 1 c.c. was given intramuscularly at weekly intervals. The diuretic response varied from 80 to 100 oz. in the 24 hours and the fluid intake was about 2 pints. Although œdema was not gross, it persisted in spite of prolonged rest and other adjuvants such as digitalis. From October 28 mersalyl 1 c.c. was injected twice weekly, and the urinary output was recorded as between 60 and 84 oz. but for one poor response of 30. During this period the fluid intake was 35–40 oz. daily. The next two injections within one week were of mersalyl in 2 c.c. dosage, and these resulted in 58 and 62 oz. in the following 24-hour periods. From November 4 the mercurial employed was neptal 2 c.c. intramuscularly twice in a week, with diuretic measurements varying between 55 and 107 oz., averaging 78, for the next nine weeks.

In January 1945 the patient's condition was much the same, but he had left bundle branch block. Neptal was continued twice weekly, preceded by three doses of 15 grains of ammonium chloride. The urinary response was recorded as varying between 40 and 100 oz. in the 24 hours, the average output being 59 oz. During that period of five weeks the fluid intake was variable, sometimes reaching 50 oz., and on one occasion 4 pints, although generally being less than 40 oz. From February 12 the injections were given somewhat irregularly, on February 19 and 21, on March 1, 9, 13, 16, 20, and 23. The diuretic response during this period varied between 55 and 66, averaging 58 oz., the daily fluid intake was fairly constant at 35 oz. and without neptal the output was 30 oz. in 24 hours.

On the day after the last injection, an erythema was noticed on the patient's feet, legs, and back. This rash was accompanied by itching and slight diarrhœa. A patch test applied three days later was found to be positive after 48 hours. His urine, usually clear, contained a cloud of albumin with granular and hyaline casts and gave a positive guaiacum reaction on March 27, but was again reported albumin free a few days later. An X-ray of his chest on March 29 showed enlargement of the left ventricle but no hilar congestion. The blood urea on April 6 was 60 mg. per 100 c.c., his blood count was later reported as 3,980,000 red cells and Hb. 80 per cent, and his plasma protein 5·4 (albumin/globulin ratio 1·7).

After a negative patch test, one further dose of 2 c.c. of neptal was given, eleven days after the last injection. There was no diuretic response (output 30 oz.), neither was there any recurrence of rash, albuminuria, or diarrhœa.

It was obvious from these investigations that the œdema was not now caused by heart failure, although initially it may have been so. The falling diuretic response to continued frequent injections of mercurial seemed to assist accumulation of the metal, and skin sensitization.

Discussion

Many patients with sustained high dosage show no signs of intolerance to mercurial diuretics; in fact, the incidence of such manifestations is rare. Numerous patients with heart failure receive full doses of neptal once or twice a week for periods of two or three years without the slightest ill effect. On the other hand, a few cases that have been reported show immediate acute sensitization to mercury, as mentioned by De Graffe and Nadler (1942). Sundaram reported sudden death in a boy of ten years with rheumatic heart disease after the first injection (0·5 c.c. salyrgan in 10 c.c. saline intravenously), but it is not yet proved that such accidents are allergic in nature.

Sensitization, idiosyncrasy, or allergy may be of different degrees. In one of our cases (Case 6) a severe skin reaction was accompanied by manifestations of an acute nephritic nature and by stomatitis. The other eight who received mercurial diuretics only gave the skin signs. It is therefore suggested that rashes and itching are evidence of a moderate degree of sensitization and might be followed by grosser complications if administration of the drug is unscientifically continued.

A positive patch test is a sign of idiosyncrasy or allergy and is accepted as such by practically all the leading authorities. According to Sulzberger (1933), " whenever a reaction of eczematous character is produced at the site of the application of the patch, provided a

substance has been used that is not a primary irritant " (presumably, in the strength employed) " one may conclude that eczematous hypersensitiveness of the skin to this substance has been demonstrated." Patients who have received mercurials for many months or years without any symptoms related to the skin have in our experience shown negative patch tests without exception. There is as yet no evidence that patients exhibiting cutaneous manifestations of intolerance are patch test negative before starting treatment. A routine patch test in a series of cases before injections are started, would decide this point; but, although primary idiosyncrasy has been reported, it is expected that such initial investigations would support the theory of acquired sensitization in the majority of cases. There would appear to be a threshold of concentration of mercury in the blood below which no signs of allergy are given, but above it they are positive. One of the earliest works on sensitization to drugs was by Jadassohn of Breslau, *A Contribution to the Study of Dermatoses Produced by Drugs* (Translation, 1900). It pays much attention to the cutaneous complications of mercurial treatment. In the main, little changes have occurred in the principles underlying the phenomenon of sensitization set out in that work, reference to which proves of great interest in this present problem; for instance, " the remarkable fact already confirmed from observation on the action of mercury and other remedies, that at first a certain cumulative action was necessary to bring out, so to speak, the idiosyncrasy . . ." Similarly, Bloch, quoted by Goldsmith (1936) wrote " idiosyncrasy is only a relative term depending not only upon the nature of the substance but also on its concentration." That accumulation of the drug in the body precedes skin sensitization, as suggested by Barber (1938), seems likely from the consideration of our own cases which tend to show a common factor, namely deficient elimination compared with the amount of drug administered. This may be caused by high or too frequent dosage, as in Cases 1, 2, 5, and 9, and assisted by renal impairment from long standing nephritic damage as in Cases 2 and 7 or from congestive changes as in Case 8, and possibly in Cases 3 and 4. Prolonged administration naturally must tend to produce accumulation of the drug; although with good diuretic response and suitable dosage it is our experience that this factor alone seldom leads to sensitization from the mercurial diuretics. The degree of susceptibility, however, must vary with each patient; for instance, in Case 6 although the previous injection had produced 120 oz. of urine and the patient was still grossly œdematous, the next injection caused an allergic reaction affecting the skin, kidneys, and mouth. Also, we have as yet no conclusive evidence that a good diuretic response assists the elimination of mercury. Quantitative estimations of this substance in the blood and urine are desirable.

From our observations it would appear that sensitivity, as shown by patch testing, may be lost after a brief period of rest from the drug and without desensitizing doses. This fact was noted by Jadassohn who remarked " cases are reported that seem to prove that idiosyncrasies may disappear in the same way as they have been acquired." Goldsmith (1936) was also of this opinion and he wrote " phases occur in specific super-sensitiveness in which the exhibition of allergen no longer causes any material effect." That transient conditions, such as threshold concentration and renal impairment, play a part is also suggested by this author's comment that " allergic disorders depend on other factors, often temporary ones, besides specific sensitization." So far, we have not met the patient who required densensitizing doses of mercury such as those employed by Tate and Klorfajn (1944) with sulphonamides.

Sensitization of one tissue to a substance contained in the body is not necessarily accompanied by a similar condition in other tissues. In our investigation we have employed the patch method of testing for cutaneous sensitivity. Our technique has been as follows. A small square of gauze dressing, about one inch wide and four or five layers thick, is soaked in the test solution (full strength neptal supplied for intramuscular injection) excess of which is expressed. This patch is placed on the skin, and covered by a larger square of dry lint, the two then being held in position by a still larger piece of elastoplast. Thus if the adhesive substance causes any irritation, the resulting cutaneous change will not be contiguous with the central square of positive reaction but separated from it by a normal area protected by lint.

It will be seen from our case reports that a positive patch test was not always obtained at the onset of itching or a rash. Case 6 exhibited a negative reaction on the arm to a patch

applied 24 hours after the onset of the abdominal rash although a positive was produced in the scapular region 48 hours later. Perhaps this observation may have been the result of a technical error. In all the other cases tested, a positive patch test followed the cutaneous symptom although such tests often became negative before the skin was clear.

The patch test would seem to have a useful application, in the treatment of patients with heart failure by mercurial diuretics. In no patient under our observation has an injection of a mercurial diuretic caused a rash when a patch test immediately preceding it proved negative. Accordingly this test should be useful when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

In conclusion, it is suggested that cutaneous sensitization to mercury need not contra-indicate the subsequent employment of these diuretics in adjusted dosage after a short interval.

Summary

Nine cases of skin reactions to mercurial diuretics are presented.

Many patients with sustained high dosage show no signs of intolerance to mercurial diuretics.

Sensitization, idiosyncrasy, or allergy may be of different degrees. Skin rashes and itching without other complications would seem to indicate moderate sensitivity.

There would appear to be a threshold concentration of mercury in the blood, above which signs of allergy develop, and this may vary with the individual patient.

Accumulation of the drug is assisted by excessive dosage, poor diuresis, and renal impairment.

The patch test is useful in determining the presence of sensitivity of the skin, especially when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

The occurrence of cutaneous complications does not preclude further use of mercurial diuretics in adjusted dosage once the phase of sensitization is past.

Our thanks are due to Dr. Horace Evans for allowing us access to the notes of Case 7, to Dr. Edith Blakely for some details of Case 3, to Dr. I. Gordon for Case 9, and to Dr. William Evans for Cases 3 and 4, and for his advice and interest in this subject.

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THE EFFECTS OF EMETINE ON THE HEART

BY

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The toxic action of emetine on the myocardium in experimental animals is well recognized, but there are conflicting reports on the frequency with which a toxic action occurs in man during the treatment of amœbic dysentery. Manson-Bahr (1939) states that emetine may produce cardiac irregularity and a fall of blood pressure. On the other hand, Brown (1935) at the Mayo Clinic states that myocardial damage is rare, and Heilig and Visveswar (1943) who studied the electrocardiographic changes following the intravenous injection of emetine in 31 cases found no signs of cardiac irregularity, extrasystoles, or heart block. They describe frequent lowering of the T waves in one or more leads, with occasional inversion of T III and T IV.

In the present investigation, changes in the electrocardiogram, blood pressure, and heart rate were studied in patients under treatment for amœbiasis. The patients were otherwise healthy soldiers between the ages of 20 and 40, and in none was there any evidence of wasting or marked toxæmia. In most cases, the standard Middle East Forces treatment for amœbiasis was followed —emetine, 1 grain, intramuscularly, with 2·5 per cent quinoxyl retention enemata, daily for 10–12 days, followed by carbasone, 0·25 g., twice daily for 8 days, and then emetine bismuth iodide, 3 grains each night, for 10 nights. The patients were confined to bed while receiving emetine and emetine bismuth iodide, and serial blood pressure readings were taken during the course. Cardiograms were taken before and immediately after the emetine injection in 32 cases, and before and after emetine bismuth iodide in 8 cases (4 of these had previously received a course of emetine injections and the cardiograms had returned to normal before the emetine bismuth iodide was commenced). It was considered that the influence of quinoxyl could be ignored, as similar changes in the cardiogram occurred when emetine was given alone or combined with the quinoxyl enemata. Owing to shortage of paper, the rate of return to normal of the cardiogram was studied in 8 cases only.

Findings after Emetine

The cardiographic changes in 32 cases following the injection of emetine (total course 8–12 grains) are summarized below.

P wave	No change	21 cases
	Increased amplitude	3 ,,
	Decreased ,,	8 ,,
P–R interval	No change	20 ,,
	Increased amplitude	12 ,,
QRS complex	No change	24 ,,
	Decreased amplitude	7 ,,
	Increased ,,	1 case
T wave	No change	6 cases
	Diminished in one or more leads	25 ,,
	Increased ,, ,, ,,	1 case

Blood pressure. Serial estimations of blood pressure were made in 21 cases. In 13 there was no significant change. Six showed a transient fall of from 15 to 20 mm. in the middle of the course, but had regained their initial blood pressure at the end. In only two cases was there a persistent fall in blood pressure during treatment.

Pulse rate. This showed no significant change in any of the patients under observation.

Findings After Emetine Bismuth Iodide

The cardiographic changes in 8 cases following administration of emetine bismuth iodide by mouth (total course 30–36 grains) are summarized below.

P wave	No change	7 cases
	Increased amplitude	1 case
	Decreased ,,	—
P–R interval	No change	1 ,,
	Increased amplitude	7 cases
QRS complex	No change	5 ,,
	Decreased amplitude	3 ,,
	Increased ,,	—
T wave	No change	—
	Decreased amplitude	7 ,,
	Increased ,,	1 case

There was no significant change in either blood pressure or pulse rate in any case during treatment with emetine bismuth iodide.

Discussion

The cardiographic changes produced by emetine and emetine bismuth iodide are similar. Owing to incomplete disintegration of some brands of the latter supplied, it has been our custom to divide the tablets to ensure that they are dissolved in the alimentary tract, and the occurrence of nausea or vomiting 4–6 hours after administration, suggests that absorption of the emetine has taken place.

The most striking effect on the cardiogram has been the diminution or inversion of the T waves during treatment. This may occur in one or more leads, and is illustrated in Fig. 1 and 2. An increase in the P–R interval of from 0·02 to 0·04 sec. was observed in 19 cases in all, but in no case did the P–R interval extend beyond the upper limit of normal. Changes in the P waves were small and infrequent.

The rate of return to normal of the cardiogram was followed in 8 cases. Changes in the T waves and P–R interval had disappeared in 8–12 days after the completion of treatment in all cases and there was no evidence of residual myocardial damage.

In this series of cases, and in over 250 cases of amœbiasis treated in this hospital, the authors have seen no clinical evidence of myocardial insufficiency during emetine treatment. In this connection it must be stressed that the type of amœbic dysentery encountered in New Zealand troops in the Middle East and Central Mediterranean Forces has been mild. None of our cases has shown evidence of malnutrition or toxæmia, and in all cases the initial

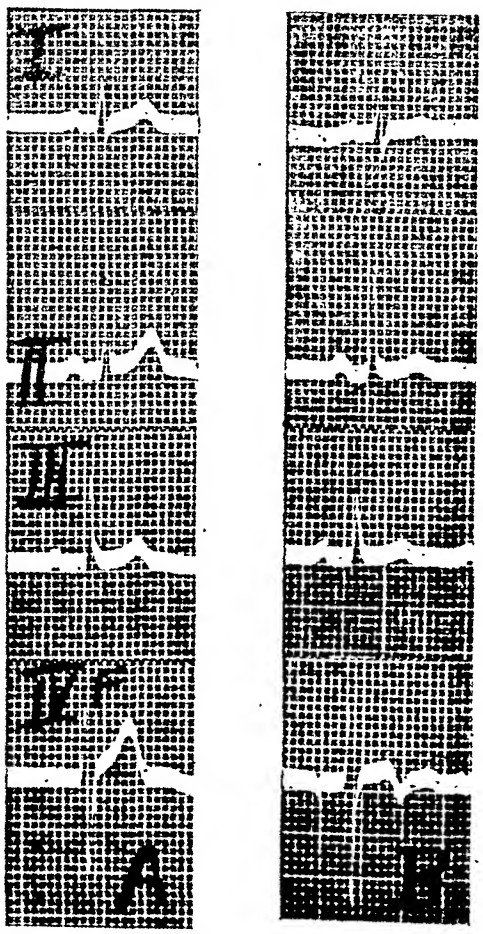

Fig. 1.—Electrocardiograms before and after treatment. Case 16. (A) October 14, 1944, before treatment. (B) October 26, 1944, after emetine, 1 grain for 10 [illegible] of T I, T II, and T III [illegible] of T IV.

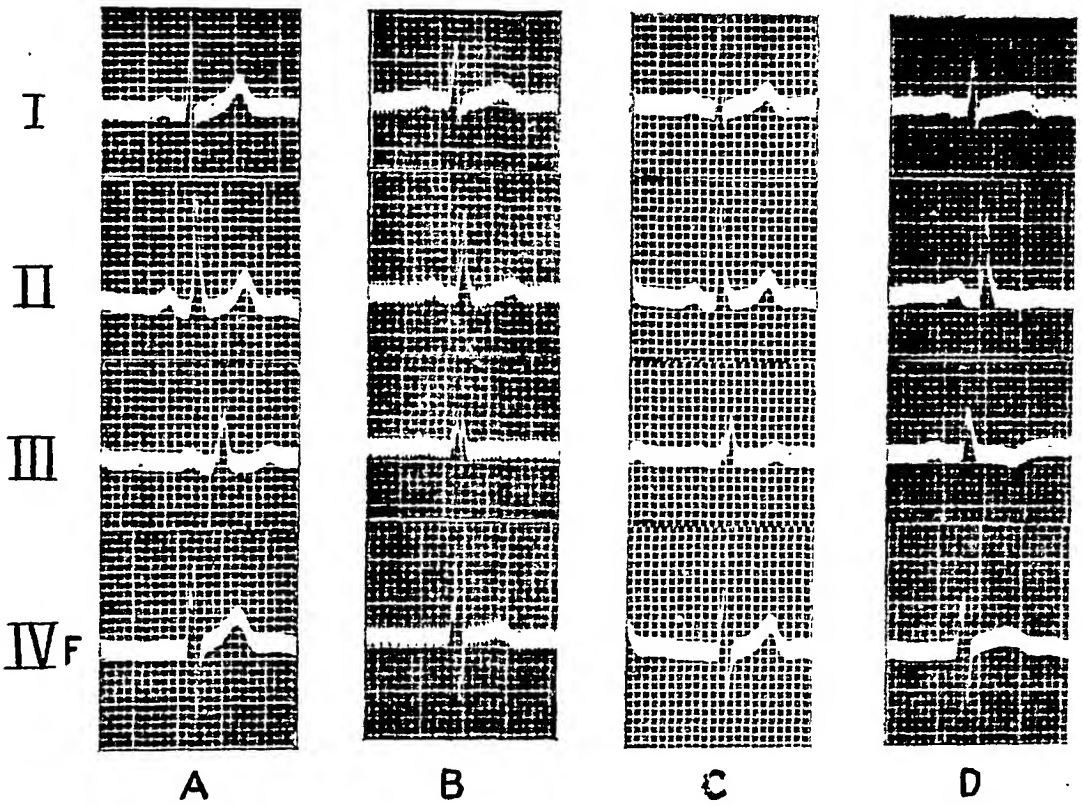

FIG. 2.—Electrocardiograms before and after treatment. Case 16. (A) April 2, 1945, before treatment. (B) April 15, 1945, after emetine, 1 grain for 10 days, showing flattening of T waves in all leads (C) April 24, 1945, showing T waves returning to normal. (D) May 7, 1945, after emetine bismuth iodide, grains 3 for 10 days, showing flattening of T I, T II, and T IV with inversion of T III, and decreased amplitude of QRS in all leads.

cardiogram was normal. Our experience is in agreement with that of Brigadier Bedford, Consulting Physician, Middle East Forces, who, in a personal communication, states that he knows of only one certain case and one doubtful case of toxic action of emetine on the heart occurring in that Command up to the end of 1944.

SUMMARY

Changes in the electrocardiogram, blood pressure, and pulse rate produced by emetine and emetine bismuth iodide have been studied in soldiers under treatment for amœbiasis. All were otherwise healthy and the initial cardiograms were normal. Diminution or inversion of the T waves occurred in one or more leads in 25 out of 32 cases receiving emetine and in 12 cases there was an increase in the P–R interval of from 0·02 to 0·04 sec. Similar changes occurred during treatment with emetine bismuth iodide, 7 out of 8 cases showing diminution in T waves and prolongation of the P–R interval. The cardiogram returned to normal 8–12 days after the completion of treatment. The effect on the blood pressure and pulse rate of both drugs was insignificant, and in no case was there any clinical evidence of myocardial insufficiency.

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THE CAROTID SHUDDER

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The diagnosis of aortic stenosis in the presence of aortic incompetence needs to be strengthened. A rough systolic murmur in the aortic area is not always accompanied by a thrill. Again, a thrill in the neck cannot be accepted as evidence of aortic stenosis without other supporting signs, especially if the thrill is short and the subject young when a systolic murmur is not expected in the aortic area. In nine patients in whom subsequent clinical, cardiographic, and cardioscopic examination, established the presence of aortic stenosis and incompetence, we observed a characteristic sign, which by itself permitted a diagnosis of the combined aortic lesion from inspection of the neck. At the height of the carotid pulse, large on account of aortic incompetence, we noticed a quiver or vibration which lasted for a moment only. This effect we have named the *carotid shudder* for it best describes the visual clinical sign.

We are not aware that it has been described before, but recently we have read in Paul White's book on *Heart Disease* (1931) a statement that one of his assistants had drawn his attention to a curious vibration in the neck of a young patient with aortic stenosis; there was no mention of associated aortic incompetence, and although it was implied that it was unique and not distinctive for any group of patients, it is probable that the phenomenon was the same as the one discussed here.

The sign was recorded by placing a tambour over the carotid pulsation and connecting it with a Mackenzie's polygraph. Records obtained in this way were examined alongside those obtained in healthy subjects and in patients with lone aortic incompetence or with hypertension producing a kinked carotid. The tracing in carotid shudder, of which that shown in Fig. 1 is representative, was taller than in health, but no taller than the one obtained in

FIG. 1.—Carotid arteriogram in a patient with aortic incompetence and stenosis in whom carotid shudder was observed.

lone aortic incompetence or over a kinked carotid, although it was usually broader and showed characteristic serrations from the vibration or shudder effect. Such vibration usually occurred at the height of the upstroke. None of the control cases showed all three features of the carotid shudder curve, namely tall, broad, and serrated. The tracings, however, failed to portray adequately the characteristic vibration which was so distinctive on clinical inspection of the carotid pulse.

Only a proportion of patients with conjoined aortic stenosis and aortic incompetence exhibit carotid shudder, but the fact that we were able to collect nine such cases during eighteen months emphasizes its common incidence. The clinical sign was sought in patients where aortic incompetence or aortic stenosis existed separately, but it was not found once.

Clinical examination. On further examination of the nine patients the pulse was often collapsing in character with a raised pulse pressure commensurate with the degree of aortic incompetence accompanying the stenosis. Pulsation was often obvious in the suprasternal notch, but never as prominent as in the carotid arteries. There was always a long systolic

thrill in the neck which was felt best above the right clavicle; in six cases the thrill was elicited in the aortic area as well. The apex beat was displaced outwards, and loud systolic and early diastolic murmurs could be heard between the aortic and mitral areas. The ætiology was rheumatic in eight patients and luetic in one.

Electrocardiogram. This was abnormal as a rule, and the changes included inversion of the T wave, depression of the R–T segment, and left electrical axis deviation. The signs of left ventricular preponderance were often present and consisted of left axis deviation, inversion of the T wave in lead I, and greater inversion of the T wave in lead CR_7 than in IVR.

Cardioscopy. The findings included enlargement of the left ventricle in proportion to the degree of incompetence present, outward curving of the ascending aorta, and extension of the left limb of the arc, which formed the aortic knuckle, towards the left clavicle; increased aortic pulsation produced an upward projection of this limb during systole, and displaced the main arc to the right. When viewed in the left oblique position the aortic elongation did not always raise the aortic arch as in hypertension, but it sometimes displaced the limbs of the arch apart and widened the base of the aortic triangle above (Fig. 2). In other cases

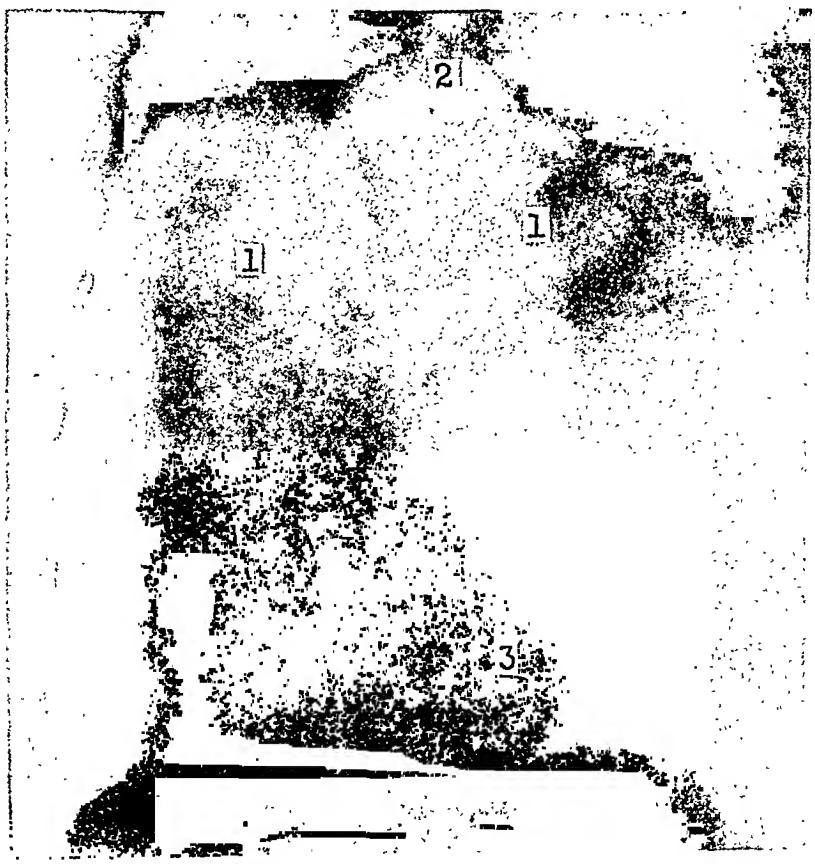

FIG. 2.—Left oblique (II) view in a male, aged 58, with aortic incompetence and stenosis, who showed carotid shudder. Elongation without elevation of the aortic arch (1) has widened the base of the aortic triangle (2). Enlargement of the left ventricle (3) is shown.

the aortic arch was neither elongated nor raised. Such effects show that the mechanism of carotid shudder is not related to any change in the alignment of the artery, but probably depends on an increase in the volume of blood discharged into the vessel with each systole and the impedient effect of the stenosed aortic valve on the returning flow to the left ventricle.

CONCLUSION

When the increased carotid pulse exhibits vibration at the height of the systolic excursion, it signifies that aortic incompetence and aortic stenosis exist side by side. We have named this sign the *carotid shudder*, and although it is not found in all cases of aortic incompetence and stenosis, its presence is a sure indication of the dual lesion.

A QUANTITATIVE ELECTROCARDIOGRAPHIC METHOD

BY

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From the Archway Hospital, London County Council

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The sum of the numerous electromotive forces generated during the spread of the ventricular impulse can be regarded as a vector quantity and represented by a straight line of certain length and direction. The angle made with the horizontal by the projection of this vector on to the frontal plane is known as the electrical axis of the heart and can be calculated, by the method of Einthoven *et al.* (1913), from the magnitude of the initial ventricular deflections in two of the limb leads of the standard electrocardiogram.

It is possible to apply this method to an electrocardiogram derived from three points in the sagittal plane of the body, thus identifying in a similar way the sagittal projection of the same vector. From these two projections on to planes at right angles to each other, both the direction and magnitude of the vector itself can readily be calculated.

The present investigation is concerned only with the magnitude evaluated in this way, and was undertaken to explore the possibility of obtaining quantitative information on the state of the ventricular muscle. The values obtained are empirical, as only a small and unknown proportion of the total electromotive force generated by the heart is induced at the periphery and becomes available for measurement. It is not, however, unreasonable to assume that, if obtained under standard conditions, these values will bear a fixed relationship in the same patient to the resultant potential difference generated during ventricular systole.

The Sagittal Electrocardiogram

The derivations of this cardiogram must be so chosen that the projection obtained from it of the vector on to the sagittal plane is concordant with the frontal projection given by the limb tracings. The triangles formed by vertebra prominens, xiphisternum, and sacrum, and by the xiphisternum, twelfth thoracic vertebra, and forehead, were tried and found unsatisfactory in this respect, probably because the xiphisternal point is too close to the heart. A sagittal tracing derived from the triangle formed by the manubrium sterni, fourth thoracic spine, and left leg, with the terminals R.A., L.A., and L.L. connected in this order was found to be suitable and was generally adopted. In this triangle the horizontal lead lies in the same plane as lead I of the standard tracing, and it is also convenient in operation, as the five electrodes for the two cardiograms can be applied at the same time and the change-over effected by a double-pole double-throw switch. As the vector is usually directed downwards and backwards, this arrangement of the terminals gives positive deflections in each of the leads, which will be referred to as A, B, and C respectively. Standard electrodes and Cambridge jelly were used for all the skin contacts.

Calculation. The symbols I, II, III, and A, B, and C, will be used to denote the positive height, in millimetres, of the initial ventricular deflections in the respective leads, or the algebraic sum where the deflection is diphasic.

Fig. 1 shows an imaginary rectangular prism, with faces lying in the frontal, sagittal, and horizontal planes, constructed about the diagonal AG, which represents, in direction and length, the apparent electrical vector of the heart. AF and AC show the sagittal and frontal projections of this vector. Now the length AG is equal to the square root of the sum of the squares on the three dimensions of the prism. The horizontal dimensions AE, AD, have

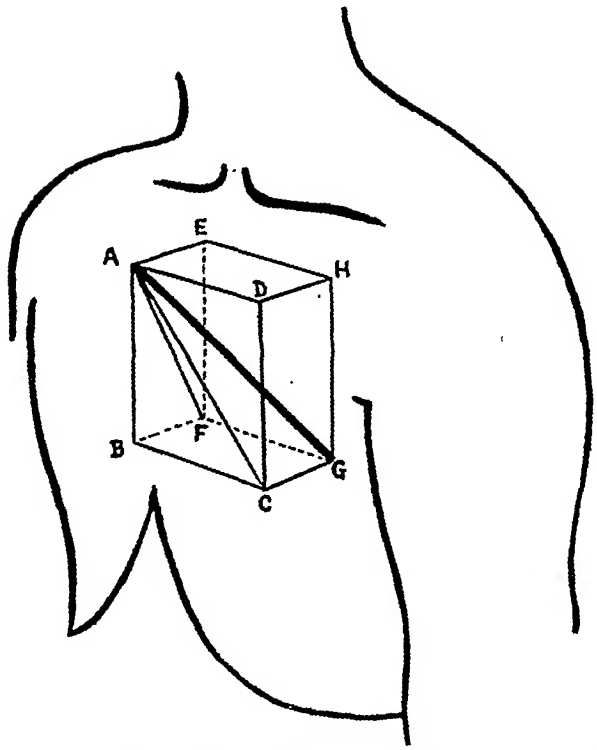

FIG. 1.—The electrical vector and its projections on to the frontal and sagittal planes.

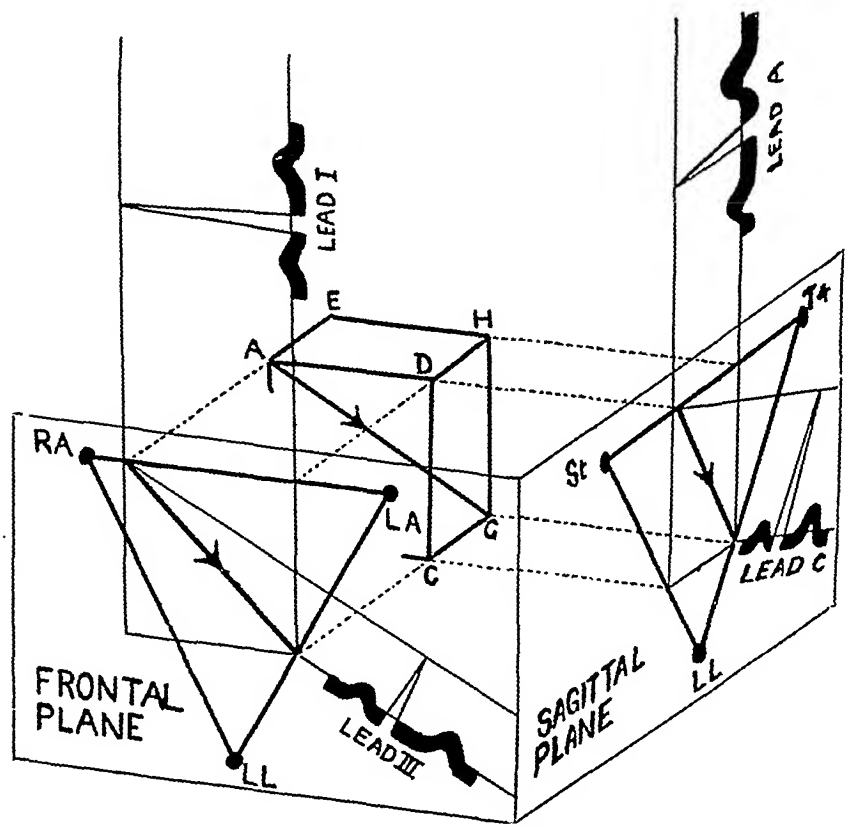

FIG. 2.—Illustrating the construction on which the calculation of V is based. The triangles are equilateral and the lettering A–G corresponds to that in Fig. 1.

the numerical values A and I respectively, and the vertical AB can be calculated from either cardiogram (see Fig. 2) as $\frac{I+2III}{\sqrt{3}}$ or $\frac{A+2C}{\sqrt{3}}$. Hence the length of the vector (V) is:—

$$\sqrt{I^2+A^2+\frac{(I+2III)^2}{3}} \quad or \quad \sqrt{I^2+A^2+\frac{(A+2C)^2}{3}}.$$

These alternative formulæ can be used to check the accuracy of the recordings in a given case. Exact agreement was not expected for several reasons, both theoretical, as the method attempts to simplify very complex phenomena, and practical, such as inaccuracy of standardization, artefacts of various kinds, and respiratory variations in amplitude.

In the 188 pairs of recordings considered here, substitution into the second of these two formulæ gave a higher value for V than was obtained from the first in 56 per cent, equality to the nearest mm. in 30 per cent, and in 14 per cent the first formula gave the higher result. If the difference exceeded one-fifth of the higher figure, the maximum that could be attributed to the summation of instrumental errors, the result was discarded. This occurred in 16 (8·5 per cent) of the cases. Otherwise a mean value for V was taken if any difference existed.

A second check can be made by recording all six leads of the cardiograms instead of only three (I, III, and A or I, A, and C) required for the calculation; inaccuracies of standardization can then be detected by substitution into the formulæ I+III=II and A+C=B.

The usual standard fibre sensitivity of one centimetre deflection to the millivolt was used, but for convenience the values V are expressed in millimetres.

Findings in Normal Subjects

Sagittal and limb tracings were recorded in a series of 50 healthy men and women between 18 and 70 years of age, and the value of V calculated in each. Lying between extremes of 6 and 26 mm., these showed a peak incidence at 11–15 mm., thereafter falling off towards the higher values (see Fig. 3). A figure below 10 mm. was found in only two of these normal subjects; in one of them it was 9 mm., and in the second (6 mm.) the tracings showed an unusual mode of spread of the contractile stimulus through the ventricles. It was not found possible to establish any relationship between an individual's V value and any other physical characteristic such as age, height, weight, height/weight ratio, body surface area, or the size of the heart as estimated by the frontal X-ray area.

Tracings, which were discarded as unreliable by the standards indicated above, were obtained from a further 6 normal subjects. Most of these showed evidence of faulty recording, but their V values, approximately estimated, were found to fall in the same groups of maximal incidence as the rest, and their inclusion would not alter the balance of the chart.

The value of V was not found to change in the same normal subject at different times or at varying pulse rates.

Findings in Abnormal Subjects

The double electrocardiograms were recorded in a series of 101 consecutive patients who were known to have some cardiac disorder and the value of V calculated in each. These cases were as follows :

Rheumatic valvular disease	32
Coronary arteriosclerosis	21
Cor pulmonale	11
Cardiovascular hypertrophy	11
Senile myocardial degeneration	4
Thyrotoxic heart disease	4
Failure associated with anæmia	4
Acute (non-rheumatic) myocarditis	3
Pulmonary embolism (without valvular disease)	2
Syphilitic coronary stenosis	1
Beri-beri	1
Unclassified	7

Ninety-one of these patients were further classified into four grades according to the severity of their symptoms.

0. Symptom-free patients, in whom heart disease was discovered during routine examination.

I. Mild symptoms; e.g. reduced exercise tolerance, or first hæmoptysis in mitral disease.

II. Moderate symptoms; e.g. early congestive failure, or repeated anginal attacks.

III. Severe symptoms; e.g. bedridden patients with advanced failure.

These results, with an analysis of their statistical significance, are given in the table and frequency distribution charts below, where it will be seen that the abnormal cases as a whole show much lower values than are found in health. Taking 10 mm. as a critical point, 45 per cent of the patients give figures below this level, as against 6 per cent of the normal subjects. It is also apparent that the tendency to provide lower V values increases with the severity of the symptoms, and that those patients who are symptomless or only mildly incapacitated show no significant variation from the normal mean. Cases of rheumatic valvular disease and coronary ischæmia have been tabulated separately to show how this tendency is increased in these groups.

TABLE I

ANALYSIS OF FINDINGS IN 151 SUBJECTS

	V value in mm.						Number of cases	Mean V value	S.D. of mean	Difference from normal mean ±S.E. of difference	Degree of significance
	0–5	6–10	11–15	16–20	21–25	26–30					
Normal subjects	0	3	22	16	8	1	50	16·2	4·5		
Abnormal—											
All cases	13	32	35	15	4	2	101	11·7	5·2	4·5±0·83	5
Grades of severity (see text) * I	1	3	8	5	2	0	19	14·4	5·0	1·8±1·31	—
Grades of severity (see text) * II	6	13	19	7	1	1	47	11·6	5·4	4·6±1·02	4
Grades of severity (see text) * III	5	11	4	1	0	0	21	8·2	4·0	8·0±1·08	8
Rheumatic V.D.H.—											
All cases with symptoms	2	8	13	3	2	0	28	12·1	4·9	4·1±1·12	3
Grades of severity 0	0	0	1	2	0	1	4	19·5	4·5	−3·3±2·32	—
Grades of severity I	0	1	4	2	2	0	9	15·8	3·9	0·4±1·41	—
Grades of severity II	0	5	7	1	0	0	13	11·5	2·9	4·7±1·01	4
Grades of severity III	2	2	2	0	0	0	6	8·0	3·9	8·2±1·71	5
Coronary disease—											
All cases	5	7	5	3	1	0	21	10·6	4·8	5·6±1·23	4
Grades of severity I	0	1	1	1	0	0	3	13·0	4·2	3·2±2·45	—
Grades of severity II	2	2	4	2	1	0	11	12·6	4·8	3·6±1·58	2
Grades of severity III	3	4	0	0	0	0	7	5·9	2·4	10·3±1·10	9
Cor pulmonale	2	6	3	0	0	0	11	8·5	3·4	7·8±1·19	7
Failure with hypertension	1	2	10	5	0	1	19	14·1	6·4	2·1±0·86	2
Do. (uncomplicated)	1	1	4	4	0	1	11	14·5	6·9	1·7±2·17	—
Do. (other lesions present)	0	1	6	1	0	0	8	13·0	2·5	3·2±1·19	2

* 91 cases were graded: 4 in grade 0 are not included here.

This measure of agreement between the depression of V and the severity of the symptoms was not found in hypertensive patients except where other complications such as coronary stenosis, cor pulmonale, or valvular disease were present. This may be because of the greatly increased ventricular bulk in such cases, or because of the relative inadequacy of even a powerfully acting heart against the increased peripheral resistance. It is important too to note that 8 of the 19 tracings from hypertensive patients showed the broad initial ventricular deflections of the bundle branch block type. This kind of tracing presents a special source of inaccuracy, because the electromotive force is really proportional to the

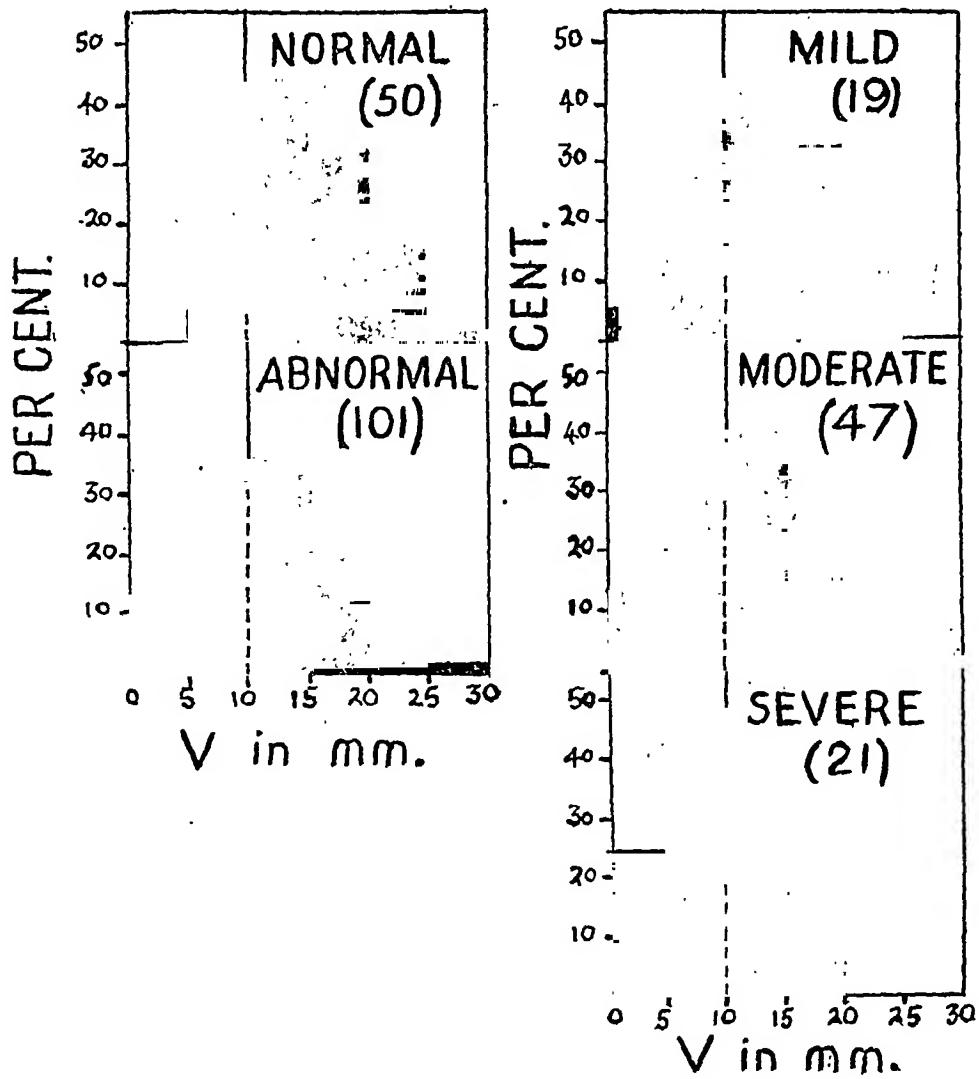

FIG. 3.—Frequency distribution charts to show the contrast between (*a*) normal and abnormal subjects, and (*b*) abnormal subjects graded by severity of symptoms. Bracketed figures show the number in each group.

area contained by the initial deflection, and the use of the linear height measurement is a convenient approximation only reliable with waves of normal duration.

Repeated evaluations of V were made at later dates in 17 of the patients in whom there was evidence that the cardiac capacity had improved or deteriorated in the interim. Of 15 patients with clinical improvement 12 showed a higher value on the later occasion, with increases up to 60 per cent of the original figure in two cases. A difference of less than 10 per cent was disregarded. These 12 cases were of diverse pathology, and three examples will be given.

1. Male, aged 60. 25/1/45. Chronic bronchitis, early cor pulmonale, B.P. 128/80. V=10 mm.

15/2/45. Much improved by rest, B.P. 155/80. V=15 mm. (+ 50 per cent).

2. Male, aged 64. 18/1/45. Pernicious anæmia (hæmoglobin 49 per cent), with congestive failure. V=5 mm.

30/5/45. Hæmoglobin 90 per cent, no evidence of failure. V=8 mm. (+60 per cent).

3. Male, aged 8. 23/5/45. Pharyngitis and cervical adenitis with toxic myocarditis, pyrexia. Cardiogram showed P–R interval of 0·24 sec., occasional sinus arrest. V=13 mm.

31/5/45. Temperature settling. P–R, 0·16 sec. V=17 mm.

7/6/45. Discharged from hospital. Normal rhythm, P–R, 0·12 sec. V=19 mm. (+45 per cent).

The last case is of interest because of the parallel recovery of the A-V block, a guide not always available in acute myocarditis.

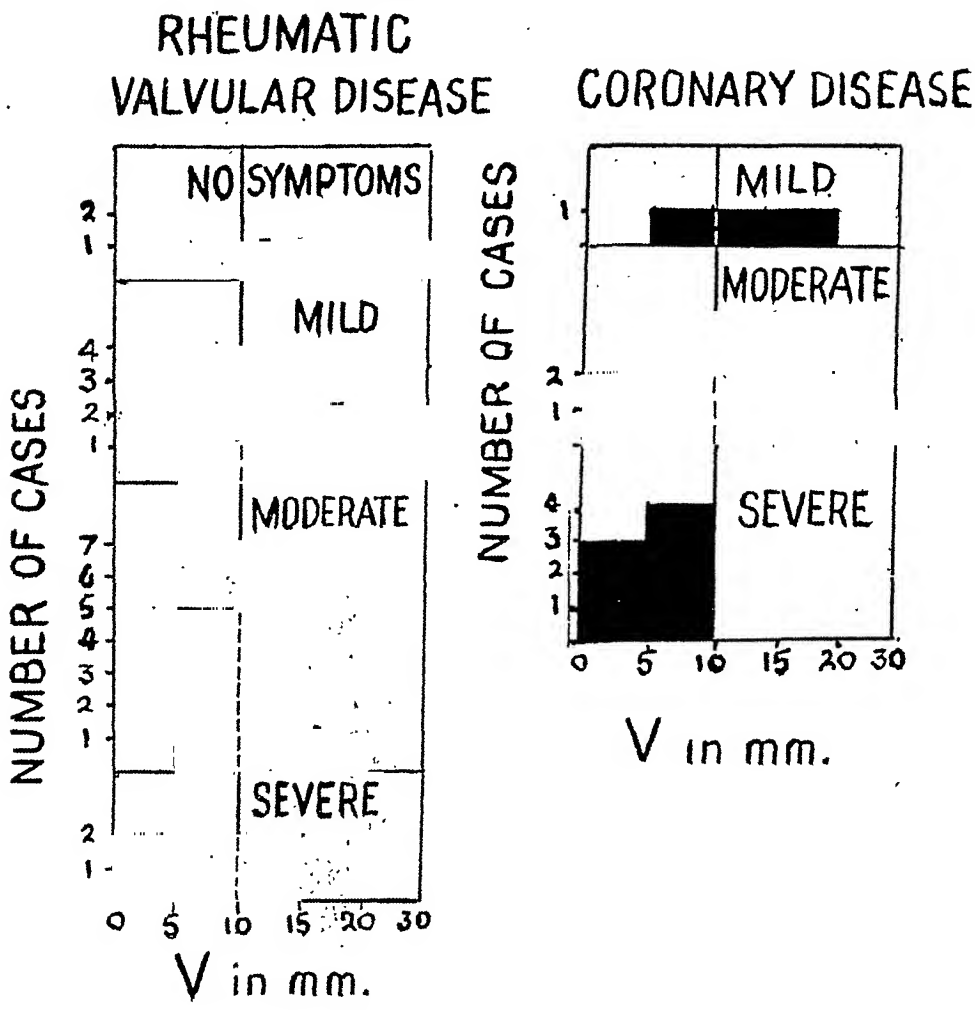

FIG. 4.—Frequency distribution in cases of rheumatic and coronary disease, graded by severity of symptoms.

Of the three cases in which the V value remained unaltered during apparent clinical improvement, one was an arteriosclerotic man of 70 with a hypochromic anæmia and bundle branch block; the second, a man of 33, where, after a coronary thrombosis one year previously, the improvement followed ambulant treatment of his œdema by diuretics; and the third, a man with Addison's disease, whose blood pressure had risen from 110/60 to 150/90 after a desoxy-corticosterone acetate implant. These patients had little in common, but it is possible that improvement in cardiac function was not the chief cause of their better health.

The two cases, both with coronary occlusion, who had deteriorated, showed falls in V of 20 per cent and 75 per cent respectively. The first presented no definite clinical change, with a variable blood pressure, but the cardiographic pattern showed regression and another occlusive attack followed three days after the second tracing.

DISCUSSION

The principal value of the clinical electrocardiogram is to provide information on abnormalities of rhythm and on disturbances of conduction of the contractile impulse. It is with the object of supplementing this by a quantitative figure based on the total resultant electromotive force generated during ventricular systole that the above method is put forward. It is realized, in the first place, that this resultant force itself, the summation of an electrical system of vast complexity, bears no well-defined relationship to the capacity of the heart to do work, and further that one measures only that proportion of the total that can be derived from peripheral electrodes. The method is therefore an arbitrary one, to be judged from a practical standpoint.

Although there is wide personal variation in the normal heart, it appears to be exceptional

for the V value to fall below 10 mm. or to exceed 25 mm. in health. There is a much wider scatter in cases of heart disease, but it is clear that low values are in general associated with increased degrees of ventricular disease or embarrassment rather than the opposite.

If, therefore, V is found to alter during a patient's illness, the direction and extent of this change might be used to assess the severity of the disease as it affects the ventricular muscle, as a measure of progress and as a guide to prognosis. Further, a rising figure during recovery from an illness may permit a retrospective diagnosis of transient myocardial damage to be made where the standard tracing has shown no abnormality. The magnitude of the variations of V observed in changing clinical states encourages the belief that myocardial involvement may be recognized in this way in cases where failure is absent and where other clinical methods give no information.

Although the direction of the vector is not discussed in this paper, it may be mentioned again here that the combination of sagittal and frontal electrocardiograms enables the observer to fix in space the vector itself instead of simply a frontal projection of it. In this way "axis deviation" in the sagittal plane can be studied. This is of value in cases of ventricular preponderance, as anatomically the main bulks of the respective ventricles lie more in a fore-and-aft plane than transversely, and the sagittal axis is less likely to be disturbed by variations in build and diaphragmatic level.

Another incidental finding in this work was the occasional elucidation of tracings that showed very small deflections in the limb leads. These low-voltage curves were twice found to be due to the rotation of the vector away from the frontal plane, so that it lay almost at right angles to it, giving in the limb leads the equivalent of a foreshortened image. One such subject showed in all the limb leads the prolonged, low, polyphasic initial deflections often attributed to arborization block. His sagittal cardiogram showed broad, high, monophasic deflections whose measurements indicated that the electrical vector was of normal dimensions but pointed directly antero-posteriorly. This suggests an explanation of the high-voltage præcordial tracings often recorded in such cases.

SUMMARY

A method of recording a sagittal electrocardiogram is described.

From the measurements of the initial ventricular deflections in this and the standard frontal electrocardiogram the magnitude and direction can be calculated of the vector quantity that represents the total electromotive force generated during ventricular systole.

The apparent magnitude of this vector in 50 normal subjects and 101 patients with heart disease is given, and the significance of the findings in various grades of cardiac disability is discussed.

The value is shown generally to rise or fall in accordance with clinical estimations of the functional capacity of the heart, where this undergoes change in the same patient.

Possible clinical applications of the method are suggested.

We wish to thank the many friends who have given their time to act as volunteers, the staff of St. Mary, Islington, Hospital (L.C.C.), where most of the work was done, for their kind co-operation, and especially Sister H. Pound for her valuable technical assistance in making the recordings.

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A CASE OF MYXOMA OF THE HEART

BY

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From the Departments of Medicine and Pathology, University of Aberdeen

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The following account of a case of cardiac myxoma is offered because of the rarity of British descriptions of this unusual condition.

A woman, aged 29, was admitted to Aberdeen Royal Infirmary on April 17, 1944, as a case of breathlessness of unknown origin for investigation. She had been a waitress for eight years and had been in good health until a year prior to admission. Since then she had suffered from breathlessness on walking, rendering impossible any additional exercise such as climbing stairs. She had associated palpitation and occasional spells of dizziness when trying to hurry. No other symptoms were complained of, and the degree of disability had not increased since its onset.

The patient was a healthy looking, well-coloured woman, afebrile, with a regular pulse varying between 68 and 92, and a blood pressure of 108/70. The apex beat of the heart was felt three and a half inches from the mid-line in the fifth left intercostal space. The mitral first sound was accentuated and followed by a high-pitched systolic murmur. The pulmonary second sound was also loud. No mitral diastolic murmur was heard, and none had been heard at the out-patient examination. The day after admission, however, a rough mitral presystolic murmur appeared and remained, the other cardiac findings being as before. Radiological examination showed definite enlargement of the left auricle, slight enlargement of the right auricle, doubtful enlargement of the right ventricle and none of the left. There were no signs of cardiac failure. Accordingly, but not without some misgivings, the condition was diagnosed as mitral stenosis, of rheumatic origin, and the patient was discharged on April 20, with advice to obtain lighter work.

On June 20, she was re-admitted with heart failure. She had rested in bed for three weeks after her discharge and had then become a sedentary worker, with a four-hour day. She had felt very breathless at work, and had experienced severe attacks of breathlessness when walking home. After five days she was forced to go to bed, where she remained, more or less constantly breathless at rest, and suffering a steady epigastric pain. About a week before re-admission, she became still more breathless, with paroxysmal nocturnal dyspnœa, following a prelude of vague lumbar and generalized pains, shivering, and feverishness.

She was distressed, cyanosed, and orthopnœic. The blood pressure was 110/84, the temperature normal, the pulse 112, regular but weaker in volume. The apex beat was now four and a half inches from the mid-line in the fifth space, and on percussion the heart appeared to be enlarged three-quarters of an inch to the right of the sternum. A well-marked rough mitral presystolic murmur and a mitral systolic murmur were present. The superficial neck veins were engorged up to the level of the angle of the jaw, the liver was palpably enlarged and tender, and œdema was present over the sacrum and in the legs; moist sounds were heard at the bases of the lungs. X-ray examination including fluoroscopy of the heart, undertaken with difficulty, showed enlargement of the left ventricle and of both auricles, especially the left, which displaced the œsophagus. An electrocardiogram showed normal P waves, low voltage of T I and T II, slight depression of S–T III, and a marked right axis deviation. Treatment with rest, light diet, restricted fluids, digitalis, and mercurial diuretics, was instituted, but apart from a slowing of the heart to normal rate, little response was

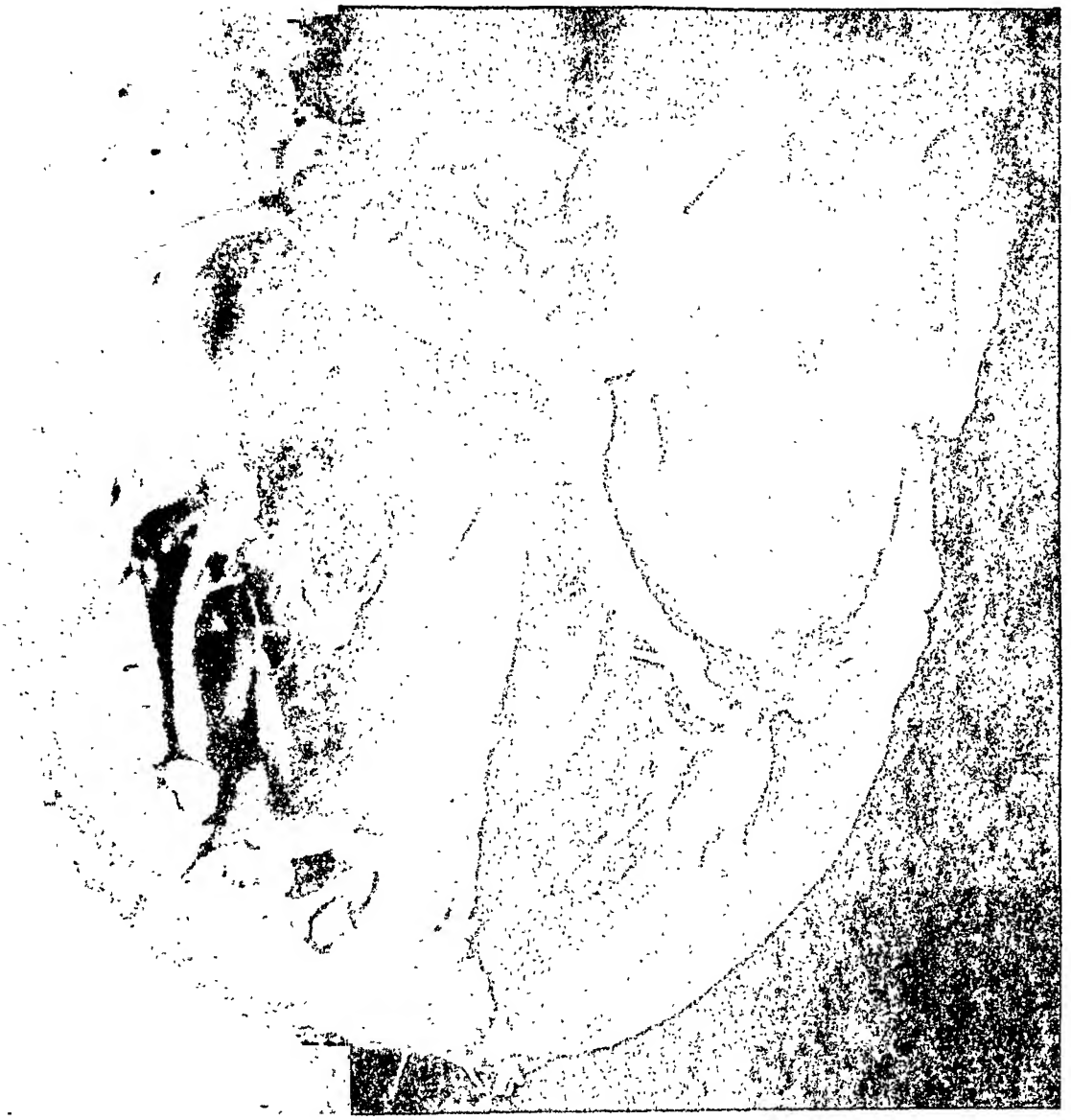

FIG. 1.—Tumour in left auricle protruding through mitral valve: pedicle attached to interauricular septum: hypertrophy of right ventricle. Natural size.

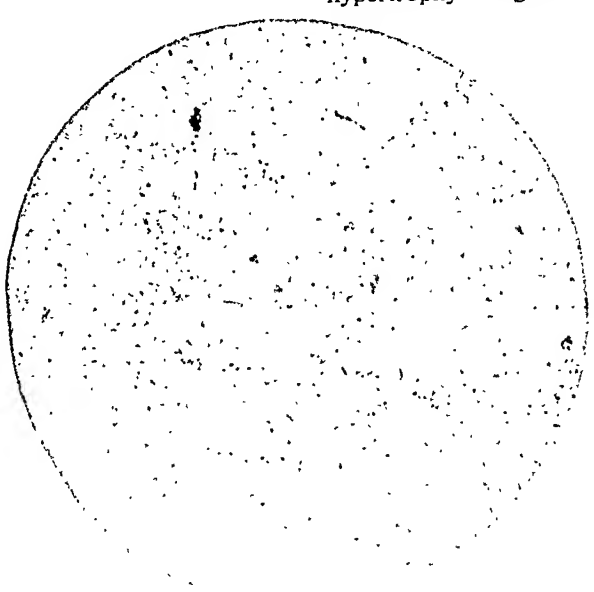

FIG. 2.—Field from tumour: abundant homogeneous matrix: scattered polymorphs and mononuclears among tumour cells. Magnification × 70.

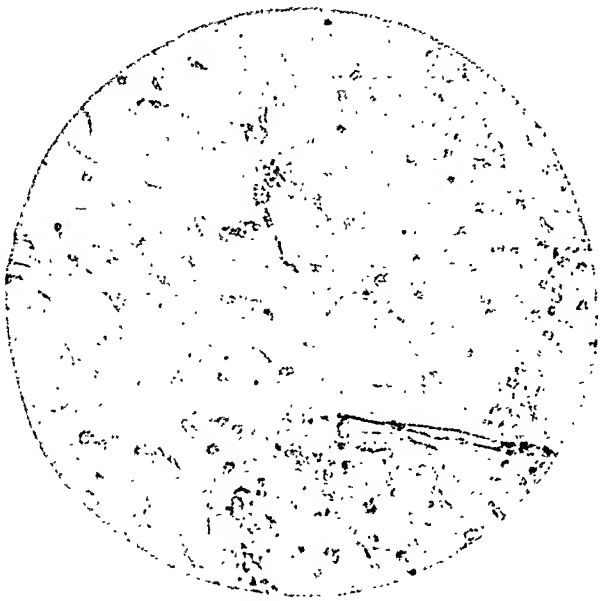

FIG. 3.—High-power view of tumour cells: thin-walled blood vessel in upper part of field. Magnification × 140.

obtained. The patient became steadily weaker, the liver increased in size with accompanying jaundice and a distressing hiccough, and infarction occurred in the right lung; finally renal secretion diminished to nothing, the blood urea level rose to 180 mg. per 100 c.c., and death took place in coma on July 6.

Examined post-mortem, the body was that of a well-developed well-nourished young female subject, showing gross œdema of the ankles and legs, marked lividity of the lips and ears and extremities, and faint icterus of the skin and conjunctivæ. The pericardial sac contained 100 c.c. of straw-coloured transudate. The heart, much enlarged, weighed 380 grams. The lumen of the dilated left auricle was almost filled by a smooth rounded tumour, 7·5 cm. × 3·5 cm. × 3·5 cm., attached to the interauricular septum; the base of the attachment was approximately 2 cm. in diameter. The tumour protruded through the mitral orifice (Fig. 1). Its cut surface was greenish semi-translucent and glistening, suggestive of myxoma, with occasional small hæmorrhages. There was no hypertrophy or dilatation of the left ventricle. The right ventricle was dilated and its hypertrophied wall was almost as thick as that of the left; the tricuspid ring was dilated. A small ante-mortem thrombus adhered to the endocardium of the right auricular appendage. The coronary arteries and the cusps of all valves appeared normal. The lungs, liver, spleen, kidneys, and other organs showed chronic venous congestion; a small recent infarct was present in the lower lobe of the right lung and another in the middle lobe.

Microscopically, the tumour was a myxoma, comprising spheroidal, spindle, and stellate cells with a very abundant homogeneous matrix (Fig. 2), staining bright pink with Southgate's mucicarmine; it possessed very numerous capillary vascular channels enclosed by a single or double layer of elongated endothelial cells (Fig. 3); occasional foci of hæmorrhage both recent and old were noted; numerous leucocytes, both mononuclear and polymorphonuclear, were dispersed through the matrix of the growth.

Summary

Cardiac myxoma was succinctly reviewed by Fawcett and Ward in 1939 and commented on by Thompson in 1944. This case belongs to the group in which, clinically, the resemblance to the picture of mitral stenosis is strong but the differences are significant. Thus the mitral diastolic murmur was inconstant, a previous history of rheumatism was lacking, the whole symptomatic course of the illness lasted less than 15 months, and the terminal heart failure developed rapidly and relentlessly, uninfluenced by treatment.

References

Fawcett, R. E. M., and Ward, E. M. (1939). *Brit. Heart J.*, **1**, 249.
Thompson, R. B. (1944). *Brit. Heart J.*, **6**, 23.

PAROXYSMAL TACHYCARDIA AND 2 : 1 HEART BLOCK

BY

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Recent work of William Evans (1944), demonstrating with chest leads that many cases of paroxysmal tachycardia have a faster auricular rate with 2 : 1 heart block and so resemble auricular flutter, demands a re-examination of our views of paroxysmal tachycardia. Evans has shown that chest leads, and in particular CR_1, are the best method of detecting the form of auricular activity, and in view of this it may seem unwise to discuss the subject further when the material available is only the standard leads.

It is, however, possible to detect some signs of 2 : 1 block in nearly half of Evans' cases using the limb lead only (see p. 194); and it may be some time before adequate evidence with chest leads can be obtained as it is easier to make the diagnosis of, than to obtain graphic records of paroxysmal tachycardia. Meanwhile, it is important that well-established clinical facts should not be lost sight of or obscured, and that until a final classification is accepted, steps should be taken to minimize any confusion that may arise among those less familiar with and less regularly concerned with cardiographic interpretation.

The present paper deals with paroxysmal auricular (or supraventricular) tachycardia where electrocardiograms of the paroxysms were available. There is enough evidence in these records to show that 2 : 1 A-V block in paroxysmal tachycardia has often been missed and is more common than has been thought, but enough to show that it is far from being the rule. Nor does the finding of 2 : 1 block in auricular tachycardia prove that the mechanism is the same as in auricular flutter with 2 : 1 block. Evans' remarks about the rate in attacks are specially discussed: there does not appear to be any exact dividing line separating the two varieties of paroxysms according to rate. This paper is based on a study of 66 cases. In the paper of Campbell and Elliott (1939) there were 42 cases with cardiograms, but 8 of these were paroxysmal ventricular tachycardia. The remaining 34 cardiograms (taken between 1925–32) and 32 others (taken between 1933–39) have been carefully re-examined for possible evidence of 2 : 1 block. The last 32 were not a consecutive series, but their selection depended entirely on which records I have been able to find under war-time conditions after the destruction of some plates by enemy action. Unlike Evans, I have not included cases diagnosed as paroxysmal auricular flutter, and 17 examples of this are discussed separately.

I have, however, realized more strongly than ever that there are cardiograms where it is not easy to make the diagnosis between paroxysmal auricular tachycardia and paroxysmal auricular flutter (Fig. 4B, 7, 9, and 11). In the course of writing this paper two cases (see Fig. 12) have been removed from the latter to the former group.

In these 66 cases 22 provide some evidence of 2 : 1 block—10 clearly and 12 much more doubtfully—and 13 provide evidence against it. During the last few months I have not been able to get a record with chest leads of a paroxysm in any of these 13 patients, but in many of them the signs of auricular activity are so clear and the spacing of the different waves so arranged that it seems impossible that these could be 2 : 1 block. In the remaining 31 (half the total) I have not been able to see any evidence for 2 : 1 block, but the mere fact that it could be hidden and is not impossible in so many cases may be held to support Evans' view that it is common, and may help to explain why it has not been recognized more often.

TABLE I

CASES OF PAROXYSMAL TACHYCARDIA WITH OR WITHOUT EVIDENCE OF 2 : 1 BLOCK

	With evidence of 2 : 1 block: favouring Evans theory		With "no evidence"	With evidence against the presence of 2 : 1 block
	+	(+)		
Series A (published) (34 cases) ..	4	6	19	5
Series B (unpublished) (32 cases) ..	6	6	12	8
Total (66 cases)	22		31	13

The differentiation of these three groups does not depend merely on the rate. In those with signs of 2 : 1 block the rate averaged 171 and varied between 144–193 (excluding the slowest and the two fastest cases). In those with evidence against 2 : 1 block the rate averaged 157 and varied between 140–176 (excluding the two slowest and the two fastest). In those without evidence either way the average rate was a little faster, 187, and twelve had rates between 200 and 240, but the remaining nineteen had rates between 145–190, the same as in the other groups. So the only conclusion that can be drawn is that if the rate is over 200 it is more difficult to see in the limb leads if there is or is not any evidence of 2 : 1 block.

PAROXYSMAL TACHYCARDIA WITH EVIDENCE OF 2 : 1 A-V BLOCK

Four of the 34 cases of my published series and 6 of the 32 of the second series provide fairly good evidence of hidden 2 : 1 block of the type described by Evans (1944) even without the study of chest leads.

The first (Fig. 6, Campbell and Elliott, 1939) has a deeper and wider S wave in lead II in paroxysms than in normal rhythm and this lies exactly half-way between the inverted P waves, showing its real nature. This is well shown in three separate paroxysms (Fig. 1A, all lead II) but is more difficult to see in leads I and III (Fig. 1B) although there is again in lead I the wider R wave without this clearly having the same significance.

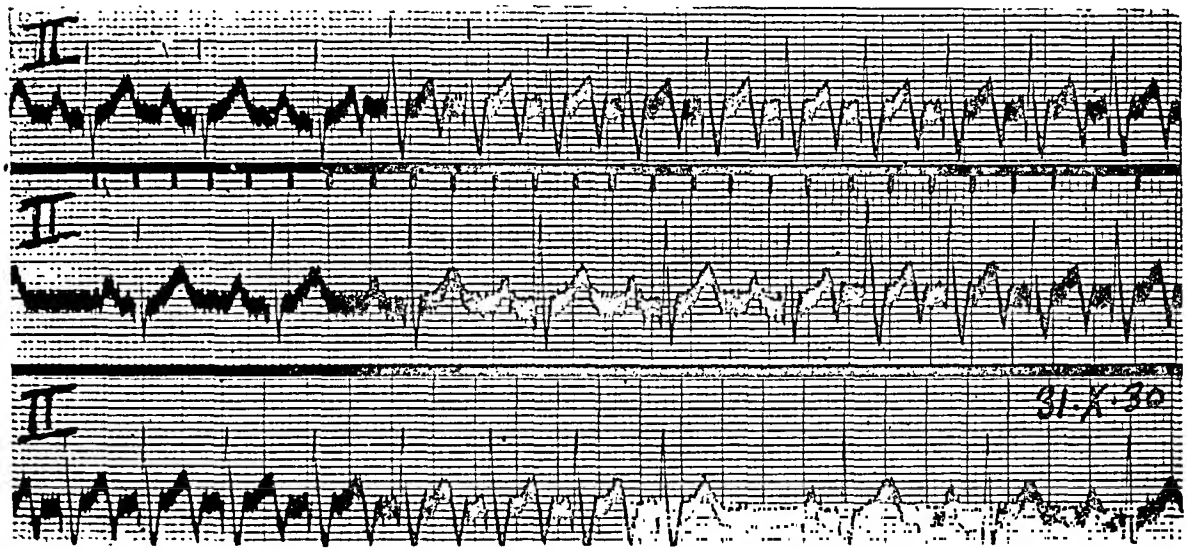
In the second (Fig. 2) the 2 : 1 block (which was missed previously) is best shown in leads I and II where parts of the alternate missing P waves have been marked in on the left of the figure. In both leads I and II it is the curved upstroke of R (occurring exactly half-way between the two easily visible P waves) that represents the fusion of a hidden P wave and an ordinary R wave.

The third (Fig. 3) is perhaps less convincing, but especially in lead II of one paroxysm and in lead III of another there seems clear evidence of a small wave at a rate double that of the ventricle. None of these three look like the ordinary curves of 2 : 1 flutter.

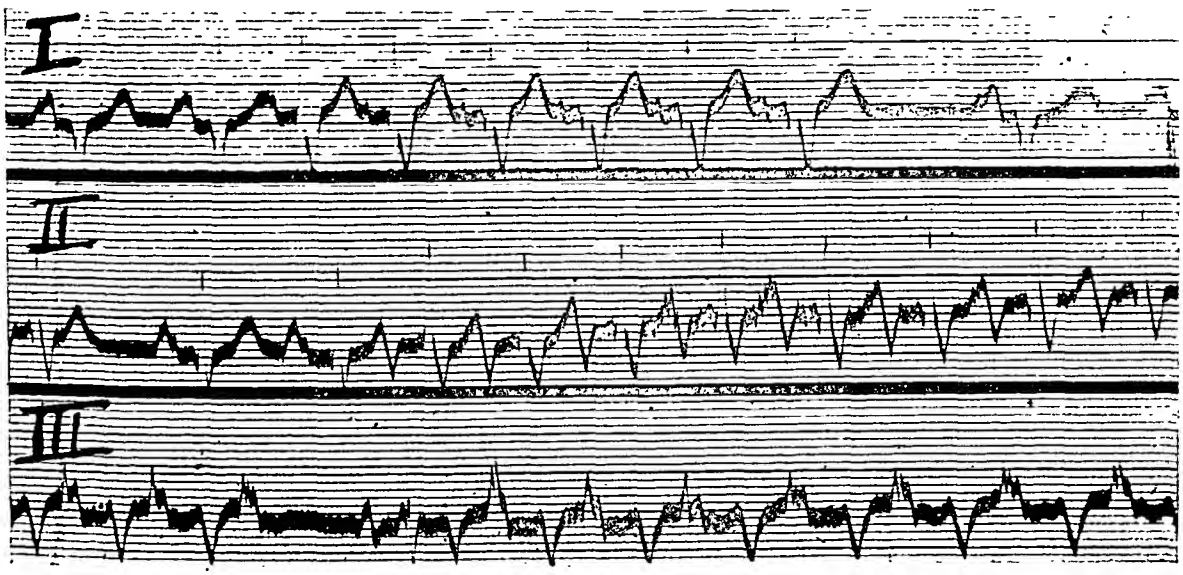
The fourth (Fig. 5, Campbell and Elliott, 1939) is best shown in the small wave coming immediately after S in lead II and in the peak just after S in lead III, both these features being absent from the accompanying record of normal rhythm and being placed just half-way between the more obvious evidence of auricular activity. This patient, aged 57 when his paroxysms started, developed established auricular fibrillation 6 years later: it is possible that his paroxysms were flutter with very poorly marked auricular waves.

The fifth case has two very different types of paroxysms in 1934 and in 1937. The former (Fig. 4A) had no very good evidence of 2 : 1 block though the points that make me think it is present have been marked. (If those who are not convinced would set their dividers for exactly half the distance between successive R waves, I think they will be surprised at how often this shorter distance seems to fit exactly on to some rather small waves that had previously seemed obscure.) The later attacks (Fig. 4B) seem to have rather clearer evidence of 2 : 1 block though the auricular waves are very minute. This is the sort of case where the chest leads would probably show the auricular activity more clearly. It is also a case where the possibility of flutter with very small auricular excursions must be considered.

The sixth case (Fig. 5) is one where I had many records taken over some years, both of paroxysms and of normal rhythm. In normal rhythm the upstroke of R II is generally notched with a rather short P–R interval and the downstroke is always sharp: in paroxysms the downstroke of R is always notched and this is exactly half-way between the most prominent wave (probably P) between the QRS waves.



A



B

FIG. 1.—Paroxysmal auricular (? high nodal) tachycardia with 2: 1 block (A, 300; V, 150) from a boy with a heart that was otherwise normal, who had frequent short paroxysms during four years' observations. Case 2.

(A) Lead II only. Deeper and wider S waves are seen in all three paroxysms exactly half-way between the inverted P waves. (B) Standard leads. The same change is readily seen in lead II; in leads I and III it can, I think, be seen but would have been more difficult to demonstrate without lead II. This and the other figures have been reduced to about 5/6ths.

The seventh (Fig. 6) is rather different. That there is some auricular activity twice as fast as the ventricular seems very obvious in any of the three standard leads, but it had not been noticed by me though perhaps it would have been by many readers. (I had not studied this record for publication in my previous series but have always been interested in all my records of paroxysmal tachycardia.) The wide notched P wave following QRS had been passed as a wide notched QRS. The P wave in normal rhythm is less notched but it is wide and the P–R interval is prolonged so 2 : 1 block is less unexpected.

The eighth (Fig. 7) and ninth are similar and without making a firm diagnosis I had thought of paroxysmal flutter with 2 : 1 block but had decided on paroxysmal tachycardia because of the shape of the curve of auricular activity. Some may think the first diagnosis was correct as there is little of the curve on the iso-electric level.

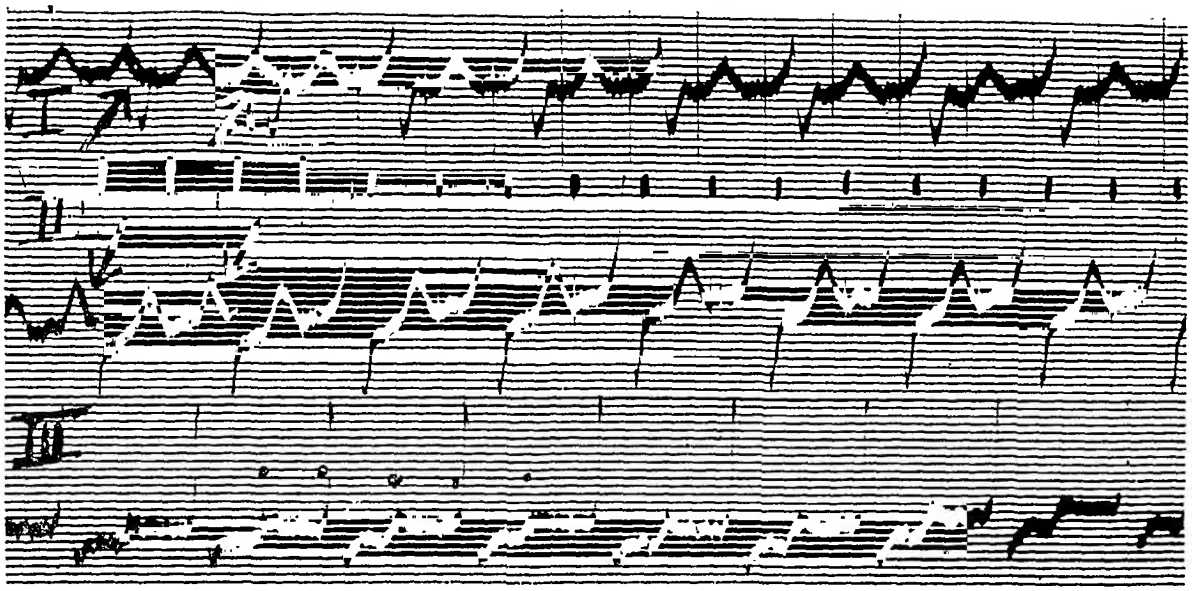


FIG. 2.—Paroxysmal auricular (? high nodal) tachycardia with 2 : 1 block (A, 300; V, 150) from a woman, aged 26–50, with mitral stenosis. Her attacks lasted up to 9 hours and came about once a month. Case 3. The second wave is partly hidden by QRS but its suspected shape has been inked in and marked with an arrow on the left of the figure.

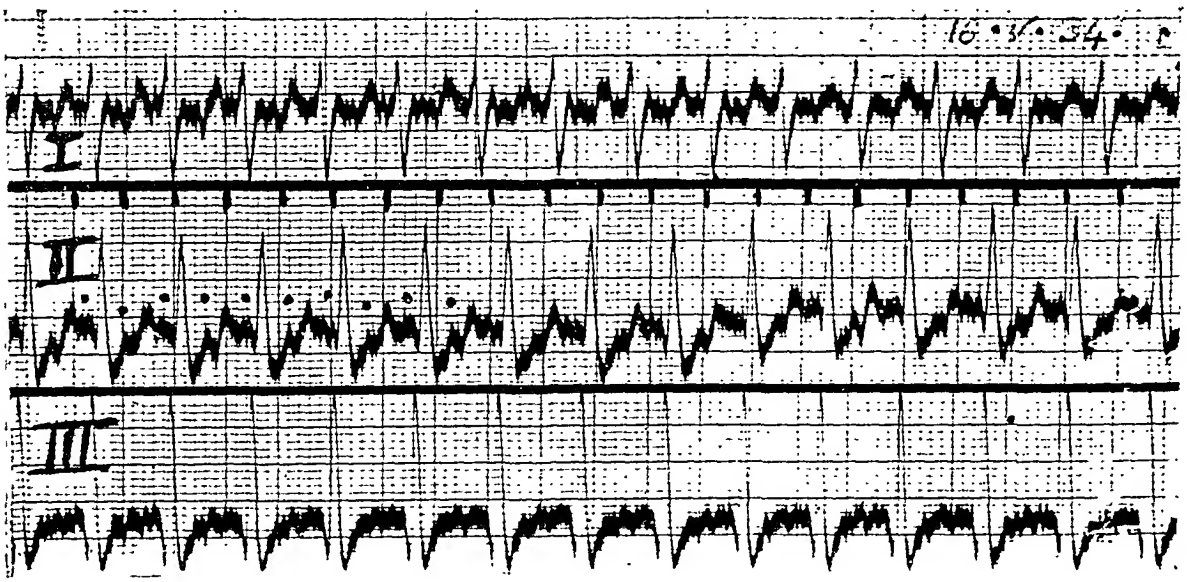


FIG. 3.—Paroxysmal supraventricular tachycardia with 2 : 1 block (A, 396; V, 198). From a woman, aged 27, with mitral stenosis who was under observation 9 years with attacks lasting from 6–48 hours. Case 84. The suspected P waves have been marked with a dot in lead II.

The tenth (Fig. 8) was (I now think wrongly) classified as paroxysmal flutter mainly because he showed at times 2 : 1 and at other times 1 : 1 block. Diagnosed clinically as paroxysmal tachycardia the first record of an attack shows 2 : 1 block (A, 222; V, 111; Fig. 8A). Although the auricular waves were not the shape of flutter I decided that the presence of block indicated this diagnosis. A few days later Fig. 8B was obtained without 2 : 1 block (A, 182; V, 182). This was certainly slow for 1 : 1 flutter which I thought it must be on the evidence of Fig. 8A, and alone it would certainly have been diagnosed as paroxysmal tachycardia.

Incidentally Fig. 8B disproves Evans' suggestion that all cases have 2 : 1 block. If 2 : 1 block is present but missed in this record, then 4 : 1 block should be present in Fig. 8A; this is obviously not so, as the curves indicating auricular activity could not be seen more clearly than they are in the standard leads.

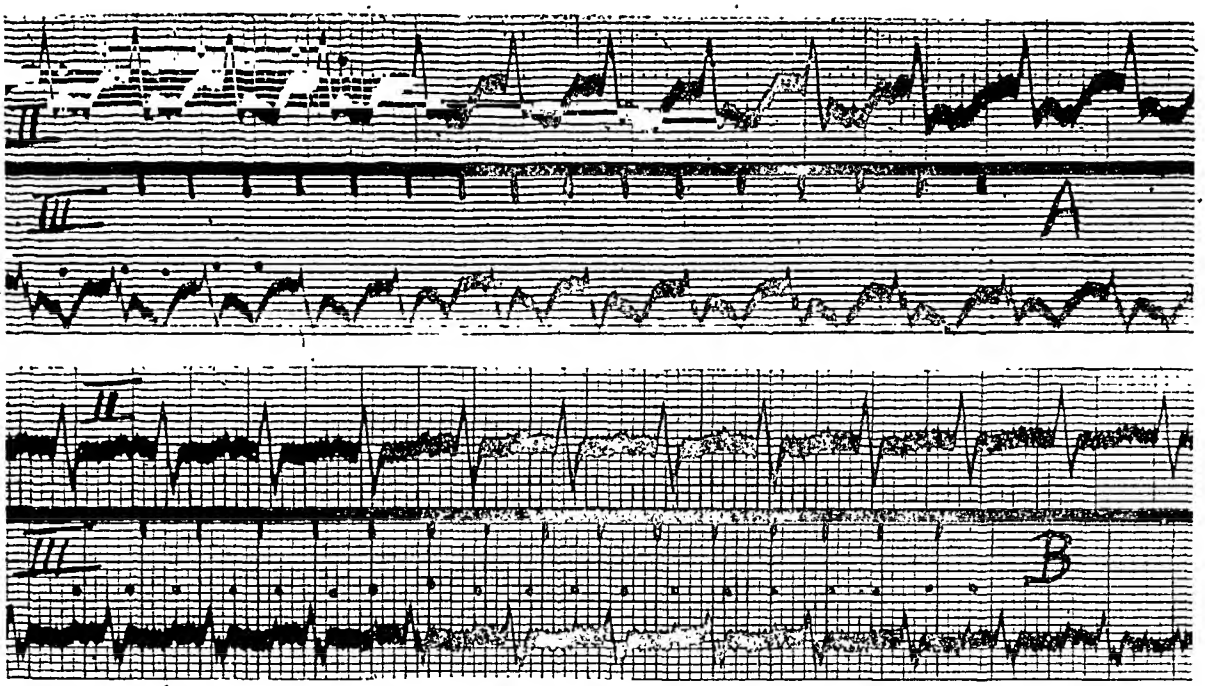


FIG. 4.—Paroxysmal supraventricular tachycardia with 2 : 1 block from a man, aged 68, with a large heart and high blood pressure, with attacks of increasing frequency lasting up to 7 days during the last 4 years of his life.

(A) 16/7/34, leads II and III. A, 332; V, 166. (B) 24/12/37, leads II and III. A, 342; V, 171. This might be flutter with 2:1 block with very low voltage auricular curves. In both cases the suspected P waves have been marked with dots.

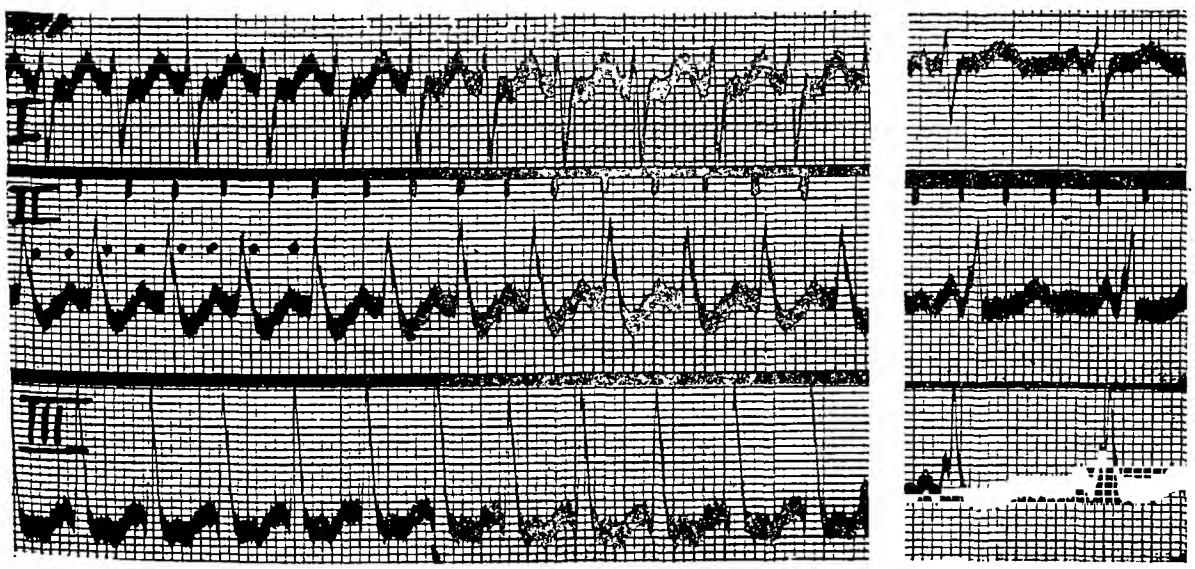


FIG. 5.—Paroxysmal supraventricular tachycardia with 2 : 1 block from a woman, aged 46, whose heart was otherwise normal. Attacks had been present for 25 years and lasted up to 48 hours.

On the right, normal rhythm. On the left, paroxysmal tachycardia (A, 386; V, 193), with the intervening P wave notching the downstroke of R in lead II and to a lesser extent in lead III.

I was reminded by these last records of an earlier one that I had put away not labelled more precisely than auricular tachycardia with 2 : 1 and 1 : 1 block (Fig. 9). I had not diagnosed paroxysmal tachycardia because the attacks were so long that it was almost if not quite the dominant rhythm during the last months of his life; but the marked waves favour this diagnosis, though the general shape of the curve resembles flutter. I have not included this case in either group.

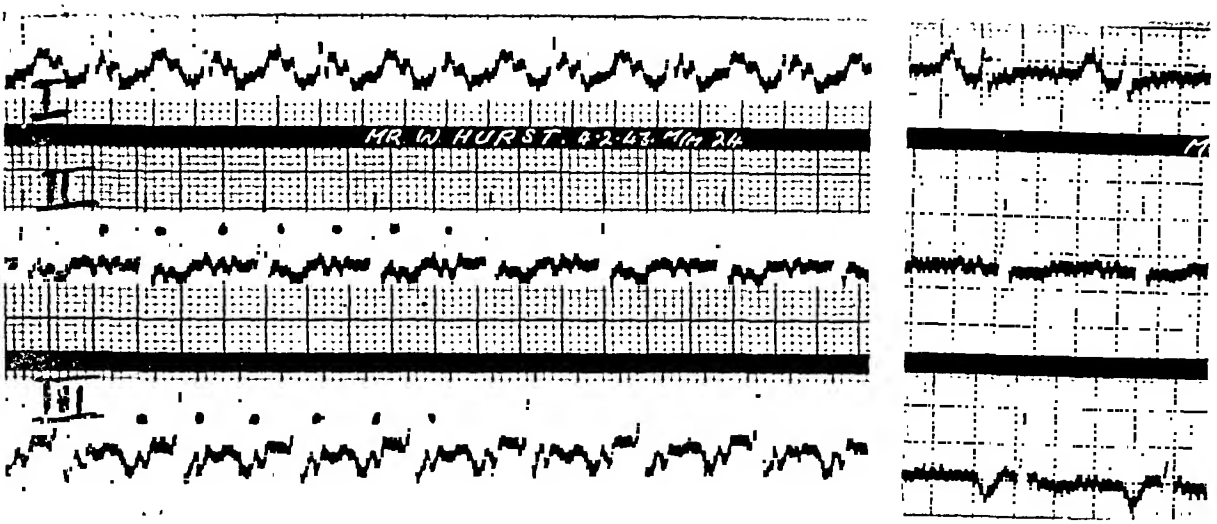


FIG. 6.—Paroxysmal auricular tachycardia with 2 : 1 block (A, 228; V, 114) from a man, aged 29, with mitral stenosis. His attacks generally lasted about 1–6 hours and had been present several years.

On the right, normal rhythm, rate 82. On the left, a paroxysm. The P waves are large and notched, even more than in the record of normal rhythm, and this produces an unusual and curious appearance of the record. It is also unusual in that the 2 : 1 block is most easily seen in leads I and III.

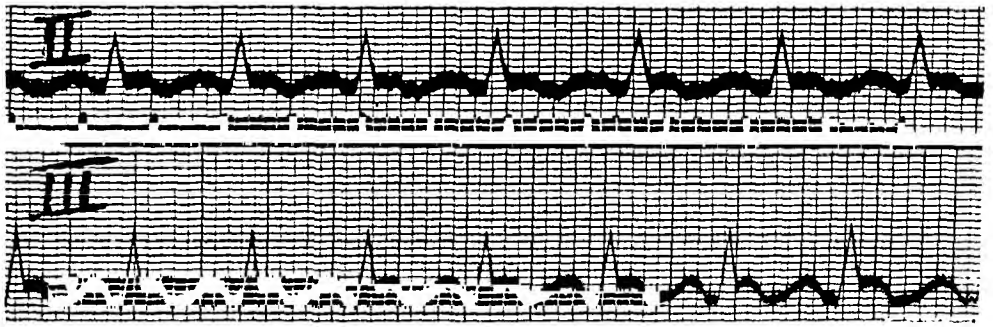


FIG. 7.—Paroxysmal auricular tachycardia with 2 : 1 block (A, 338; V, 169) from a woman, aged 50, with hyperthyroidism, and frequent paroxysms, generally lasting a few hours.

The 2 : 1 block is more obvious than in many records and paroxysmal flutter with 2 : 1 block was thought a possible diagnosis. The shape of the auricular curves (here and in Fig. 9) is somewhat like flutter, but on the whole the shape was thought to be more against than in favour of flutter.

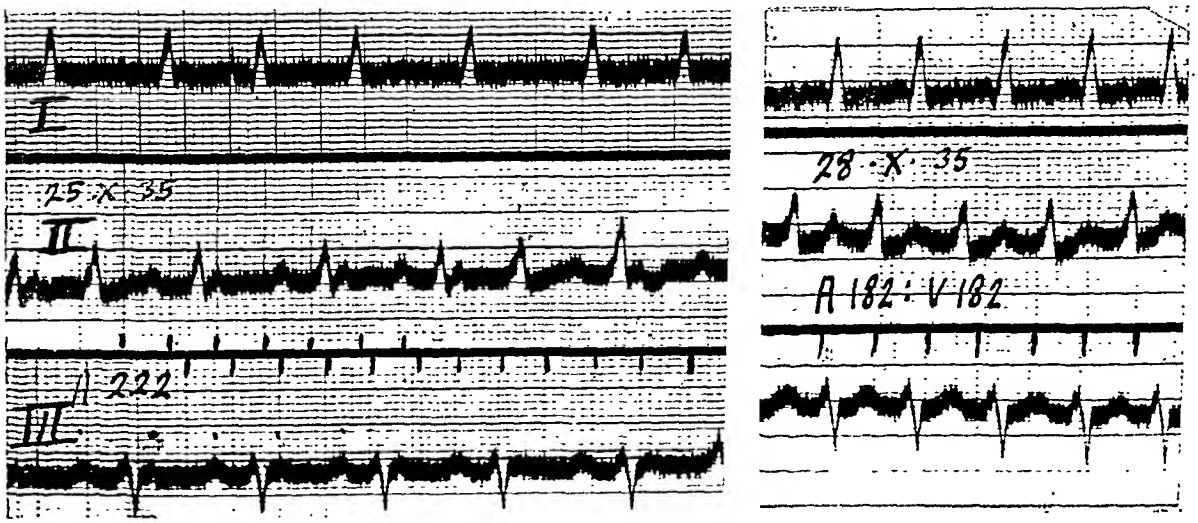


FIG. 8.—Paroxysmal auricular tachycardia with and without 2 : 1 A-V block, from a man of 44, who died with acute pericarditis and possibly syphilitic myocarditis after 18 months with paroxysms, generally lasting one or two hours.

(A) With 2 : 1 block. A, 222; V, 111. (B) Without 2 . block. A, 182 V, 182.

Fig. 8 (B) proves that paroxysmal tachycardia occurs without hidden 2 : 1 block, because if 2 : 1 block was present but hidden here, 4 : 1 block would be present in Fig. 8 (A), which is obviously not the case.

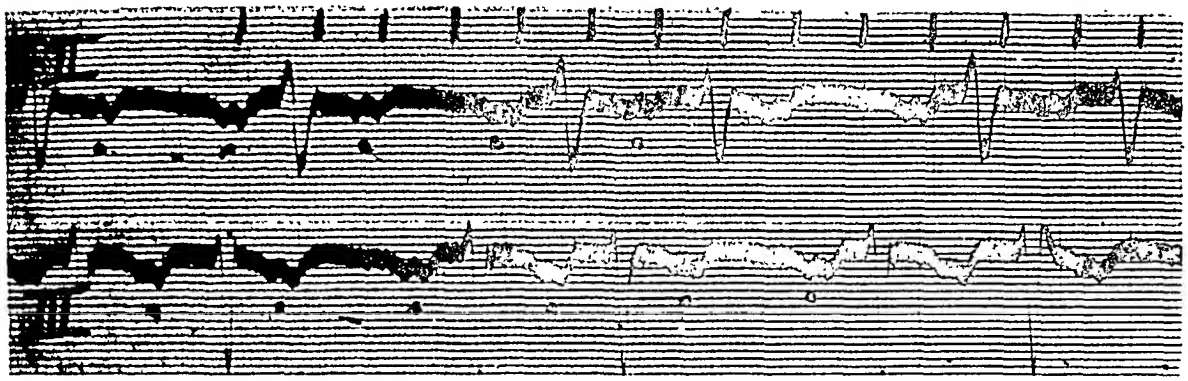


FIG. 9.—Irregular block (1 : 1 and 2 : 1) in auricular tachycardia from a man, aged 65, with myocardial disease. The case was not diagnosed as paroxysmal tachycardia, because of the block (now admitted to be an inadequate reason) and because the tachycardia was present for nearly or quite as much time as the normal rhythm. Lead II and III only.

The 12 that provide some slight evidence of 2 : 1 block need not be detailed but Fig. 10, 11, and 12 are given as examples. If the earlier 10 cases have not succeeded in convincing the reader that 2 : 1 block occurs but has been overlooked, these less striking ones will not do so: in any case a final decision as to how common the different types are will have to be reached after more detailed studies of unselected series making use of chest leads.

Fig. 10 is from a woman of 39 who had had frequent paroxysms for four years. She was obese and had a severe microcytic anæmia (Hb. 36 per cent but had been raised to 55 per cent with iron). She died from a pulmonary embolism from extensive venous thrombosis in both iliac veins. Death was during the second day of an attack but there had been other longer attacks. It is only in lead III as marked that there seemed to be some evidence of 2 : 1 block.

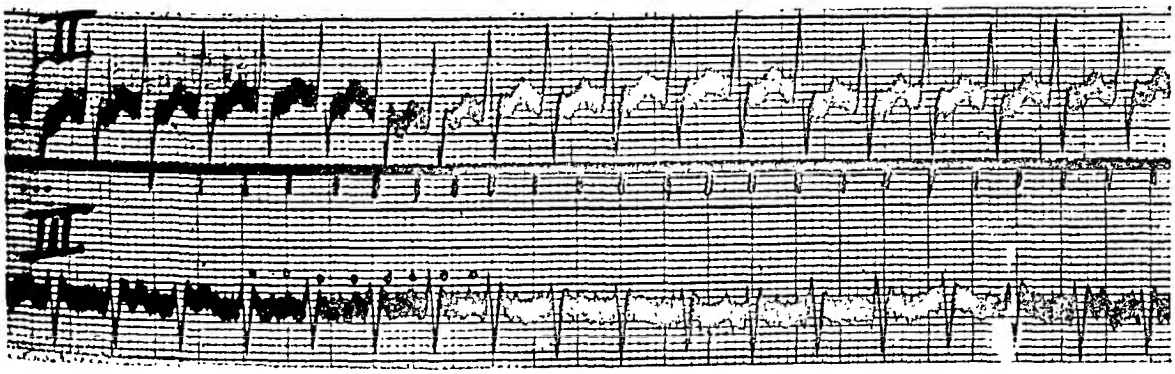


FIG. 10.—Paroxysmal supraventricular tachycardia with possible 2 : 1 block. Ventricular rate 200 (see text). Leads II and III only.

Fig. 11 has perhaps a little more evidence of 2 : 1 block as marked in leads II and III. The only known paroxysm followed a gastrectomy for a fibro-sarcoma of the stomach in a man of 61; the rhythm changed to fibrillation after seven days and then to normal rhythm with digitalization.

Fig. 12 shows a paroxysm—the only known one in a woman, aged 48, who had been under observation for twelve years with bradycardia and cardiac enlargement of unknown origin. She was in hospital at the time with bronchitis and threatened left ventricular failure. Generally she had left ventricular preponderance with rather wide QRS waves but not the picture of bundle branch block as during the attack. This was a record first diagnosed as paroxysmal tachycardia, then (on evidence of lead II) as paroxysmal flutter with 2 : 1 block, and finally again as probable paroxysmal tachycardia.

Fig. 13 (here) and Fig. 4 and 18 (Campbell and Elliott, *loc. cit.*) may be taken as examples of curves I have classified as " no evidence." I can find nothing to suggest that there is 2 : 1 block but the main waves R and T or R and P are so spaced that they could hide such evidence if it was present.

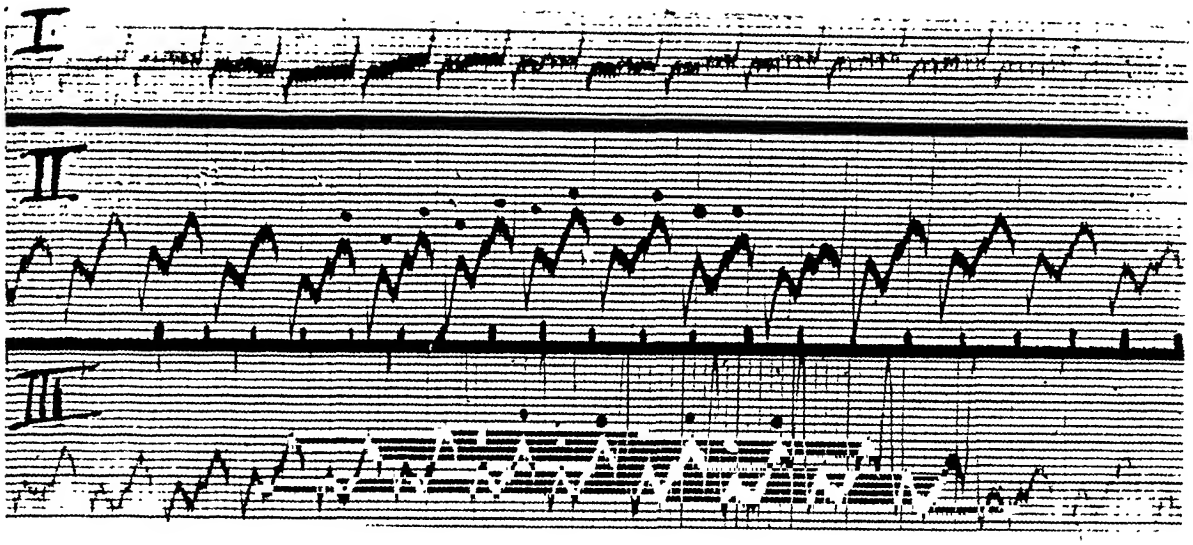


FIG. 11.—Paroxysmal supraventricular tachycardia with possible 2 : 1 block. Ventricular rate 166 (see text). Owing to the shape of the curves of auricular activity, it is more difficult to exclude auricular flutter with 2: 1 block in this case.

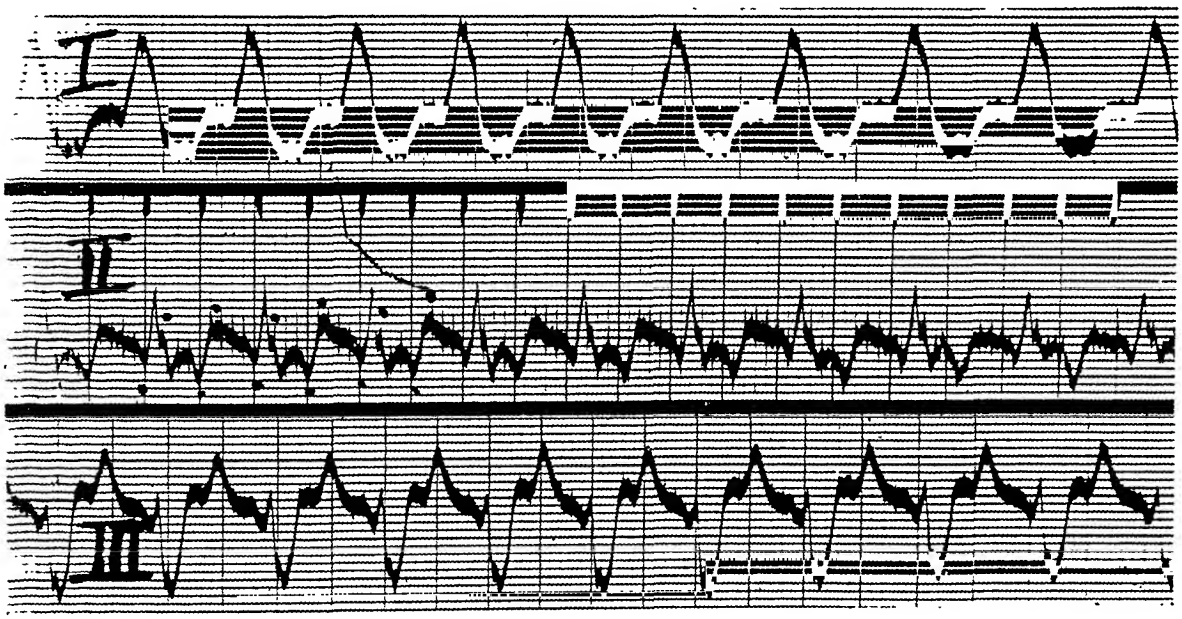


FIG. 12.—Paroxysmal tachycardia, ventricular rate 148 (see text).
It is thought to be paroxysmal auricular tachycardia with bundle branch block and 2 : 1 block; but a diagnosis of paroxysmal ventricular tachycardia or of paroxysmal flutter with 2 : 1 block (see lead II) could be made. This curve illustrates the difficulty of decisive diagnosis in such cases without other experimental observations.

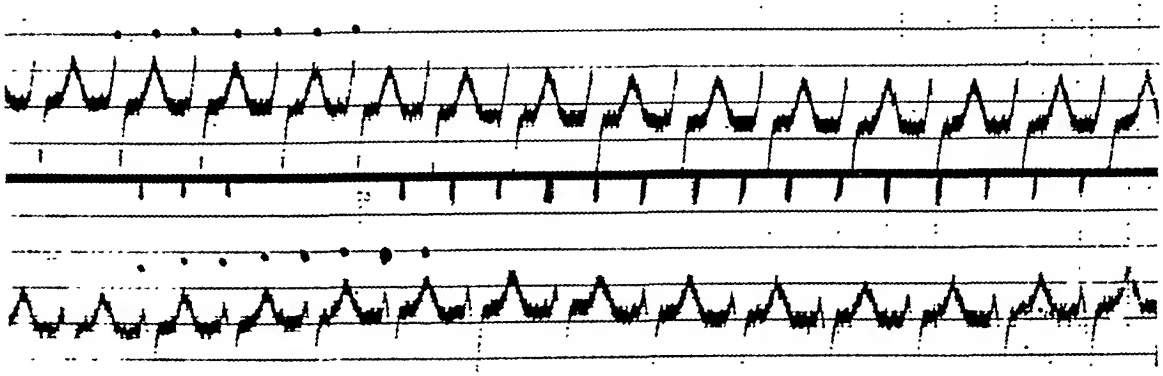


FIG. 13.—Paroxysmal supraventricular tachycardia where there is no direct evidence of 2 : 1 A-V block, but where it can not be excluded, as indicated by the dots. Ventricular rate 166. Leads II and III only.
From a man, aged 49, whose heart was otherwise normal. Paroxysms had been present for 5 years and did not generally last more than 2 hours.

Fig. 13 is from a patient whose attacks were clinically ordinary paroxysmal tachycardia: there is no positive evidence of 2 : 1 block but the sharp tip of the T wave is so exactly halfway between the rather broad R that P waves might be hidden at one or both of these points. Half of all my cases (31 of 66) belonged to this group.

Paroxysmal Tachycardia without 2 :1 Block

In his series Evans recorded no such cases, but they appear to be fairly common—13 of the 66 cases. In these the curves of auricular activity are easily seen, and at the point halfway between these waves there is a level or nearly level iso-electric period in which it should be easy to see the second auricular wave were it present. Fig. 14 (Fig. 7 of Campbell and Elliott) is perhaps the most striking example.

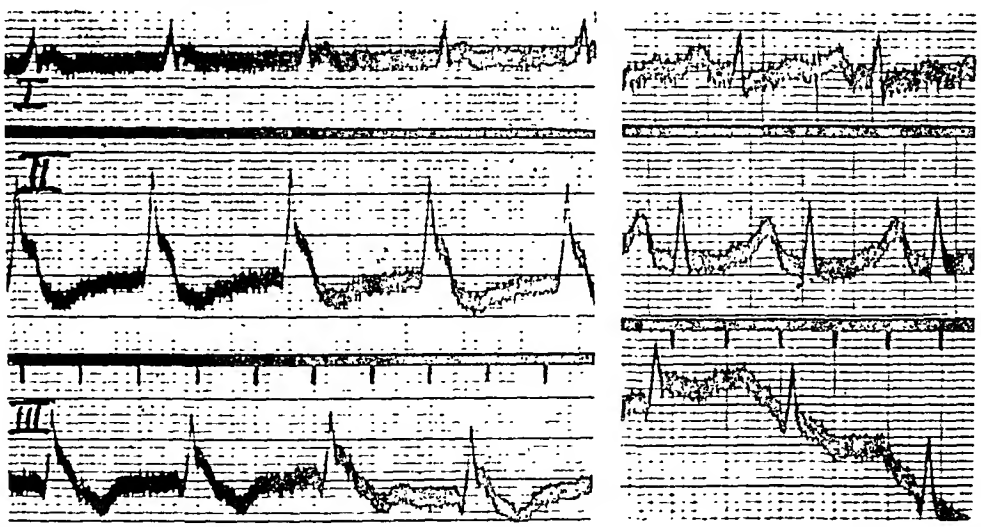


Fig. 14.—Paroxysma nodal tachycardia, rate 125, without 2 : 1 block. On the right normal rhythm From a woman, aged 27, with mitral stenosis (Case 87). Attacks had been present for 6 years and generally lasted less than an hour.

The ending of the large P wave is seen just on the downstroke of R, especially in lead II, and there could not be 2 : 1 block as such a large wave could not be missed elsewhere in the record.

Three other examples of different types of supraventricular paroxysmal tachycardia are illustrated. In Fig. 15 the P–R interval is normal in the paroxysm in lead II but the P wave is fairly deeply inverted—the type that I have called " high " nodel. A second P wave, if it

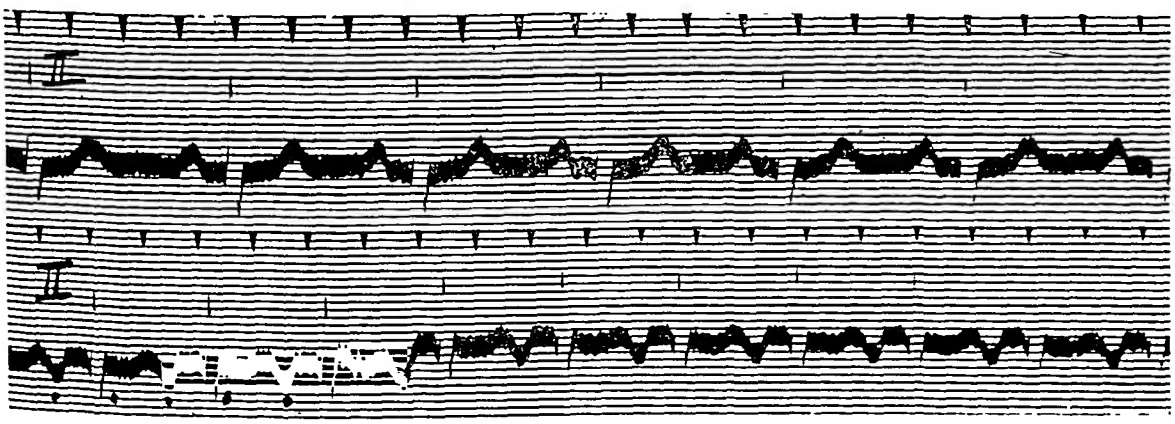


Fig. 15.—Paroxysmal " high nodal " tachycardia without 2 : 1 A-V block (below); and normal rhythm (above). From a woman, aged 34, with frequent short attacks whose heart was otherwise normal. Case 22. Lead II only.

The spacing is such that a second inverted P wave would be easily visible after QRS, were it present.

were present, would be easily seen in the smooth iso-electric S–T period shortly after S (marked with a dot).

Fig. 16 has an inverted P wave shortly after QRS—a typical example of nodal tachycardia. If a second P wave were present it should be easily seen in the level period just before QRS

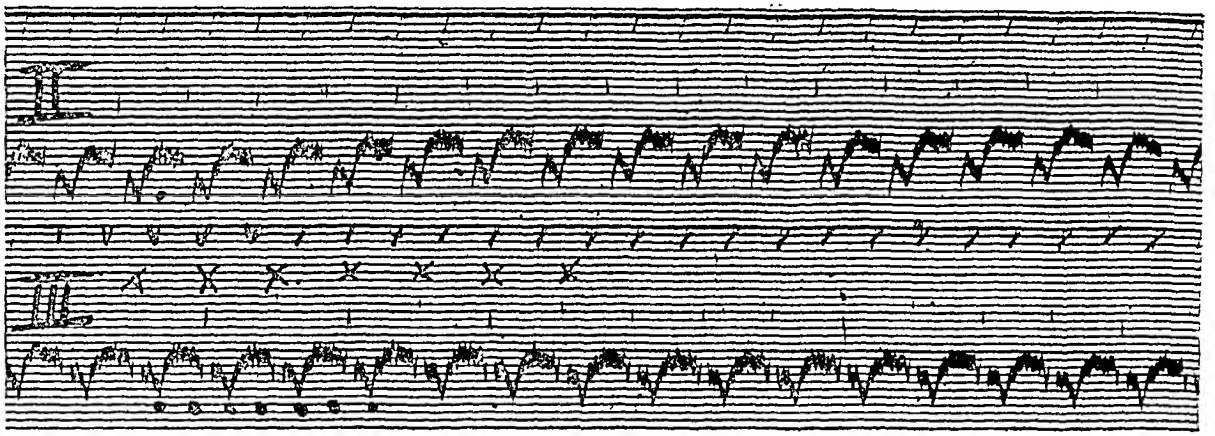


FIG. 16.—Paroxysmal nodal tachycardia without 2 : 1 A-V block. From a woman, aged 53, with a heart that was otherwise normal and frequent paroxysms lasting up to half an hour over a period of 36 years. Case 42. Leads II and III only.

The spacing is such that a second inverted P wave would be easily seen before QRS (as marked with dots), were it present.

in either lead II or III, and as there is no deformity there it is certain that 2 : 1 block is not present in this case either. If the rate happened to be a little faster the hypothetical P wave might be present but hidden in the start of QRS and this would place the case among those I have classified as " no evidence."

Fig. 17 is auricular tachycardia at two slightly different rates so that the P wave is some-

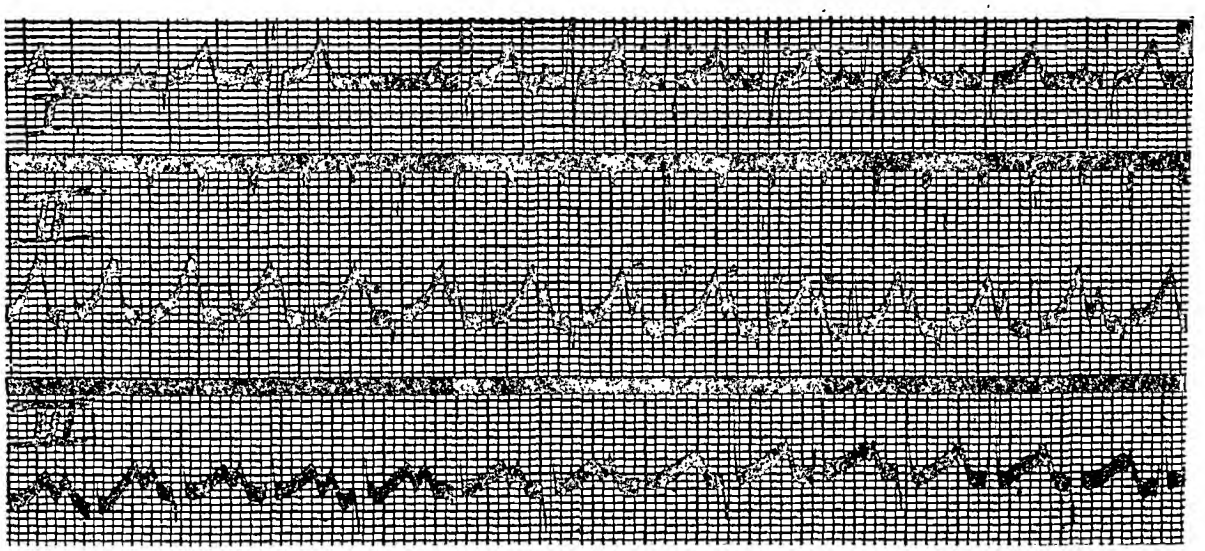


FIG. 17.—Paroxysmal auricular tachycardia without 2 : 1 A-V block. From a small child with a congenital heart (probably a ventricular septal defect with some degree of pulmonary stenosis) who had frequent paroxysms generally lasting for hours and died about a year later with pneumonia.

The spacing is such that a second upright P wave would be easily seen after QRS (as marked with dots), were it present.

times almost or quite hidden in the downstroke of the preceding T wave (rates 150 and 166). Again if a second P wave were present it should be clearly seen and could not be missed in the smooth slowly rising period shortly after S (marked with a dot).

Szekely (1944) reported some chest lead cardiograms of paroxysmal tachycardia which help to prove that 2: 1 block is not always present (his Fig. 1 and 2A). Fig. 2A is specially conclusive because Fig. 2B shows that 2 : 1 block could occur and was easy to detect in this patient (compare my Fig. 8).

It seems, therefore, that in some records of paroxysmal tachycardia, more than one-quarter, there is, even in the standard leads, some evidence of auricular activity at twice the expected rate with 2 : 1 A-V block. It is, however, equally clear that in other records, nearly one-quarter, there is decisive evidence that no A-V block is present. About the remaining half it is not possible to express an opinion without further study using chest leads.

Discussion of Evans' Cases

At first sight the findings of 2 : 1 A-V block in all of Evans' 27 consecutive cases is almost conclusive evidence that such block is present in all or nearly all cases of paroxysmal tachycardia. But examination of the cases makes this rather less certain, partly because he includes cases of flutter and partly because many of his cases are of a rather unusual type so that the series cannot be regarded as representative of paroxysmal tachycardia as a whole. Evans has kindly lent me the records of 11 of the unpublished cases so that 26 of the 27 can be discussed.

Case 6 (his Fig. 7) is certainly auricular flutter, sometimes with 2 : 1 and sometimes with 3 : 1 block. Evans agrees that by the criteria he has chosen for the selection of these cases paroxysmal flutter would be included. This also applies to his Cases 15 and 26. Case 26 is of special interest because the first record is orthodox flutter with 2 : 1 block (A, 218; V, 109) and the second shows a quite different picture at a rate of 217. Seeing this alone I should call it paroxysmal ventricular tachycardia; with the previous record it seems more like 1 : 1 flutter with bundle branch block owing to the more rapid rate. Evans regards it as 2 : 1 block in paroxysmal tachycardia (A, 434; V, 217) but his two auricular waves might be the first notch of the ventricular complex and a retrograde P wave on the downstroke of R: if he is correct it is hard to explain why there is 2 : 1 block at such different auricular rates as 434 and 218, the former showing that the ventricle is quite capable of responding at a rate of 217.

Cases 5, 9, and 14 (his Fig. 6, 11, and 14) might be regarded as flutter on the standard cardiograms. With the knowledge I have gained from Evans paper I have no difficulty in finding evidence of 2 : 1 block in leads I, II, or III (and actually it is clearer in III than in CR_1, for Fig. 11). The first two had mitral stenosis and certainly the second had not typical paroxysmal tachycardia, but the third was a woman who was otherwise healthy, with typical paroxysmal tachycardia.

Cases 1 and 2 (his Fig. 3 and 4) have not got a regular rhythm in their attacks. Even in the standard leads of Case 1, I can now find the evidence of block but it is clearer in CR_1. In Case 2, no such evidence can be found without the help of CR_1. Cases 1 and 2 on the history available do not appear typical cases of paroxysmal tachycardia especially because the arrhythmia was converted to fibrillation with digitalis in each case.

This still leaves 18 cases, including 9 of those illustrated, where the cardiograms would certainly have been passed by everyone as paroxysmal tachycardia. In 11 of them the history also is of classical paroxysmal tachycardia, but in the other 7 some question might be raised: in Case 3 because " latterly the attacks had lasted for some months," in Case 4 because they occurred during a terminal heart failure with broncho-pneumonia and were changed to fibrillation with quinidine (once); in Cases 7 and 16 because the attacks only came in the terminal stages of mitral stenosis and once (in Case 7) the rhythm was changed to fibrillation by digitalis; and in Cases 18, 19, and 23 because they occurred after cardiac infarction and in Case 18 were changed to fibrillation by digitalis; Cases 19 and 23 died within a short period.

It is, of course, true that paroxysmal tachycardia may occur for the first time in the late stages of heart failure or after cardiac infarction, and may at times change to fibrillation under the influence of digitalis; but both these events are more common with auricular flutter, and therefore such cases are not the best ones for evidence of the characteristic and common behaviour of paroxysmal tachycardia.

Even so, if one is hypercritical and rules out every case where the diagnosis might be questioned on cardiographic or more doubtfully on clinical grounds there are still 11 cases of classical paroxysmal tachycardia. In all of these 11 (except perhaps in Case 22 (his Fig. 15)

and Cases 17 and 20, not illustrated, where the evidence still seems to me inconclusive) there was certainly 2 : 1 A-V block.

For comparison with my own figures I have examined Evans standard limb lead cardiograms for signs of 2 : 1 block in the 20 cases, including 11 with published cardiograms, but excluding the 6 that are or might be flutter. In 9 there seems to be no doubt that 2 : 1 block can be demonstrated (his Fig. 3, 8, 9, 10, 13, and 21, and 3 unpublished); in 11 I should still have to mark them as " no evidence ": none are examples of the records that seem to me against accepting his view as the rule for all cases of paroxysmal tachycardia.

That, even now after familiarizing myself with the slighter indications of 2 : 1 block, I can only discover evidence of its presence in less than half the cases shows how essential a lead such as CR_1 is in assessing auricular activity in paroxysmal tachycardia.

Other Cases with 2 : 1 Block

Most other workers who have found 2 : 1 block have reported only one or two cases and therefore do no more than prove that 2 : 1 block does occur, but two papers deal with a larger number of cases and must be considered in more detail.

Barker, Wilson, Johnston, and Wishart (1943) have reviewed 35 cases of paroxysmal auricular tachycardia with A-V block, generally 2 : 1, 18 of their own and 17 that had been reported by others. They found that these attacks differed in certain ways from ordinary paroxysmal tachycardia. The attacks lasted longer, in more than half the patients for two days or more and sometimes for 26, 60, and 94 days. The disability caused by the attacks also seemed to be greater but as this would probably be diminished by the presence of 2 :1 block the explanation may be the longer attacks and the relatively high proportion with organic heart disease. Full doses of digitalis often restored normal rhythm and quinidine also did so but less often. Pressure on the carotid sinus, mecholyl, and acetylcholine were only successful in stopping attacks in one case.

Barker *et al.* stress the value of præcordial or œsophageal leads as in some cases the auricular deflections are small or not readily apparent in the standard limb leads. They emphasize that all the curves are quite different from those of auricular flutter, in that the auricular waves are separated by periods of electrical quiescence with the curve at rest on the base line. They conclude that paroxysmal auricular tachycardia with A-V block resembles auricular flutter in many respects but differs from it in some important particulars.

In a further paper Barker, Wilson, and Johnston (1943) discuss the arguments for circus rhythm as the mechanism of paroxysmal auricular tachycardia, but this paper is less pertinent to the present discussion: they suggest that the circus movement must have special features and this may be because its circulation path includes either the S-A or A-V node. Decherd *et al.* (1944 and 1945), however, adduced arguments against the rhythm being due to a circus movement.

Decherd, Herrmann, and Schwab (1943) have described 38 cases of paroxysmal supraventricular tachycardia with some degree of partial A-V block: they were selected from 102 cases of paroxysmal tachycardia and so formed a high proportion. This group of cases, as they themselves emphasize, was very unlike an ordinary group with paroxysmal tachycardia. Of the 38 cases, 55 per cent died during the period in hospital when their paroxysm with block was observed. In 35 of the 38 congestive heart failure was present before the appearance of the paroxysmal tachycardia with A-V block, 80 per cent having hypertensive or arteriosclerotic heart disease. Only 7 patients had not received digitalis and 23 had " an obvious overdosage of digitalis." In 25 digitalis medication preceeded and may have precipitated the tachycardia. Aminophylline had been given intravenously to 7 cases shortly before the attack.

Only 2 of the 38 cases had hearts that were otherwise normal and of these one had received a moderate, and the other an excessive, amount of digitalis. The ætiological factors were, therefore, very unlike that generally found in a random sample of cases of paroxysmal tachycardia. They were, in fact, nearer in many ways to the ætiological factors found with paroxysmal ventricular tachycardia. They also resembled the conditions under which partial

heart block with dropped beats occurs in patients without paroxysmal tachycardia (Campbell, 1943)—digitalis medication, sometimes in excessive doses, and infection, and often the two combined.

Decherd *et al.* emphasize that we do not possess absolute criteria for the sharp differentiation of auricular tachycardia and flutter.

Finally the 2 : 1 block found by Decherd *et al.* and by Barker *et al.* is of a different type from that of Evans. Evans' cases had ventricular rates that were normal for paroxysmal tachycardia and auricular rates twice as fast as this. The other reported cases had auricular rates that were normal for paroxysmal tachycardia and slower ventricular rates—generally half as fast as the auricular rate. Thus, in the cases of Barker *et al.* with 2 : 1 block the auricular rate averaged 189 (most cases having rates between 160 and 220) and the ventricular rate half of this. And in the cases of Decherd *et al.* the auricular rate averaged 192, and was generally between 166 and 250, and the ventricular rate was half this. In the cases of Evans, on the other hand, the ventricular rate was normal, generally between 130–250, and he suggests that the auricular rate was twice as fast as this. These data are summarized in Table II.

TABLE II

HEART RATES IN PAROXYSMAL TACHYCARDIA

Author	Auricle	Ventricle
Barket *et al.*	160–220 (average 189)	80–110
Decherd *et al.*	166–250 (average 192)	83–125
Campbell	140–240 * (average 178)	140–240
Price (1941)	120–250 (usual 160–200)	120–250
Evans	260–500 *	130–250

On the other hand, the few cases of Brown (1936) appear to have been of the same type as those described by Evans, as he thought these were 2 : 1 A-V block with auricular rates of 300 and 428.

Before discussing the subject more generally, certain conclusions from a short series of cases of paroxysmal auricular flutter will be given.

PAROXYSMAL AURICULAR FLUTTER

Under the same conditions that I have collected 66 cases of paroxysmal tachycardia I have collected 17 cases of paroxysmal auricular flutter, in each instance with electrocardiographic evidence of the attack. Those cases where all the paroxysms showed an irregular rhythm simulating fibrillation and possibly some where paroxysms occurred only for a short time before flutter became established have been excluded.

The whole clinical picture of these patients is so different from paroxysmal tachycardia that even if it was proved that the underlying mechanism of both abnormal rhythms were the same or similar, some other explanation of the different clinical pictures would be needed.

Of the 17 cases, 12 were men and 5 were women. It has generally been found that flutter is more common in men, but that paroxysmal tachycardia has about the same incidence in both sexes. The age incidence was spread from 30–74, but the only two cases under 40 had rheumatic mitral disease. Even including them, the average age *when the attacks started* was 54 and the maximum incidence was between 55–59 years of age. The age distribution of the cases if shown below, where it is contrasted with the age incidence of paroxysmal tachycardia.

TABLE III

AGE INCIDENCE OF PAROXYSMAL FLUTTER AND OF PAROXYSMAL TACHYCARDIA (AT ONSET)

	Up to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 and over
Paroxysmal auricular flutter: number of cases	—	—	—	2	2	8	4	1
Percentage	—	—	—	12	12	46	24	6
Paroxysmal tachycardia: percentage	7	16	31	22	12	8	4	—

* This over-simplifies the question because I agree with Evans that in some cases the true auricular rate is twice as fast as the apparent rate.

In paroxysmal flutter nearly all the cases started after 40 (88 per cent): in paroxysmal tachycardia most started before 40 (76 per cent).

There was an equally striking contrast in the ætiology. Half the cases with paroxysmal tachycardia were otherwise normal. Only three of those with paroxysmal flutter were without other evidence of heart disease and as these three were aged 55, 56, and 60 it is difficult to be sure that the hearts were really normal though the youngest of the three is still in good health 15 years later. The ætiological factors were as follows:

Congenital	 1	Coronary disease	 3	Chest diseases	 3
Rheumatic	 2	High blood pressure	 2	Normal (aged 55, 56, and 60)	.. 3
Thyrotoxic	 2	Heart failure	 1		

Equally striking was the difference in the length of time during which the attacks had been present before the patient came under observation. In paroxysmal tachycardia this period was often many years while in flutter it was generally not more than months or was clearly associated with some other development of the heart disease.

Only 5 of the cases had attacks that could be regarded as indistinguishable from ordinary paroxysmal tachycardia and in these they had been present for 2, 6, 9, 30, and 34 months—always less than three years. Possibly the first of these was an exception as he thought he had been cured after a year of paroxysmal tachycardia by Sir James Mackenzie, 22 years before: in the interval he had developed a blood pressure of 240/160 and had reached the age of 74.

In 4 others the attacks were generally irregular and often paroxysmal auricular fibrillation and it was only later that one or more attacks of flutter with regular A-V block were observed. The details were: paroxysms for 6 years, mostly irregular, later established auricular fibrillation; paroxysms for 4 years, nearly if not all irregular and frequently recorded as paroxysmal auricular fibrillation, good health with fewer paroxysms 12 years later; paroxysms for 5 years diagnosed as paroxysmal auricular fibrillation till a cardiogram showed auricular flutter with longish periods of regular 2 : 1 block (the irregular periods being a mixture of 2 : 1 and 1 : 1 were difficult to distinguish from fibrillation without the help of regular 2 : 1 periods); about equal numbers of paroxysms of flutter and fibrillation, both recorded, in an elderly woman with thyrotoxicosis.

In 4, the patients were already in hospital when the first attack occurred: with congestive failure; with cardiac infarction; with carcinoma of the bronchus; and with a pleural effusion. In 2 others the patient was so incapacitated by a first or by an early attack that he was taken into hospital: on the thirtieth day of a first attack with anginal pain; and on the thirty-fifth day of a third attack in a patient with angina and doubtful cardiac infarction.

In the last 2 of the 17 cases the rhythm was more like established flutter interrupted by normal rhythm: the first attack in one was stopped by quinidine after two months, and the second attack by quinidine after rather longer than this; the second had congenital pulmonary stenosis with slow flutter (A, 190; V, 95 and A, 166; V, 83) which was present as often as normal rhythm without much change in his symptoms.

Even this short account of the cases with paroxysmal auricular flutter gives a very different picture from that of a series of cases with paroxysmal tachycardia.

The Rate. In these 17 patients with paroxysmal auricular flutter the auricular rate varied between 170 and 376 * a minute; but in 13 it was between 240 and 336 and in 10 between 276 and 336.* The average rate was 290. The most usual finding was 2 : 1 block so that the ventricular rate was about half this, generally between 120 and 168. Higher degrees of block were less common though 4 : 1 block occurred with a relatively slow ventricular rate, generally in cases that were unusual in some other way also. 3 : 1 block was not seen as a persistent rhythm though it is frequently mixed with 2 : 1 or with 4 : 1 block and was observed in some of these cases when they had irregular hearts.

In Table IV, the ventricular rates in paroxysmal tachycardia and flutter are contracted and the differences are very striking; although there is much overlapping. In flutter most

* Price (1941) gives 180–360, most commonly about 300, and Conybeare (1942) gives 260–320 as the usual limits of auricular flutter.

(83 per cent) are between 120 and 180. In paroxysmal tachycardia most (88 per cent) are between 140 and 220. Or this can be expressed in another way. If the ventricular rate is below 140, flutter is more likely (2 to 1). If the ventricular rate is between 140 and 180, paroxysmal tachycardia is more likely but paroxysmal flutter is not uncommon ($3\frac{1}{2}$ to 1): but if the ventricular rate is over 180, paroxysmal tachycardia is almost certain (13 to 1).

TABLE IV

VENTRICULAR RATES IN PAROXYSMAL TACHYCARDIA AND PAROXYSMAL AURICULAR FLUTTER

	Ventricular rate							
	Below 120	120 to 139	140 to 159	160 to 179	180 to 199	200 to 219	220 to 239	240 and above
Paroxysmal tachycardia, 66 cases	1	2	16	21	9	12	3	2
Paroxysmal flutter, 17 cases	1	4	4	6	2	0	0	0
Paroxysmal tachycardia, percentage	1	3	24	32	14	18	5	3
Paroxysmal flutter, percentage	5	24	24	35	12	0	0	0

The rate of 160 is the nearest possible approach to a dividing line but it is very inexact. In half the cases of flutter (52 per cent), the rate is below 160: in three-quarters of the cases (72 per cent), of paroxysmal tachycardia, the rate is above 160, and in nearly half between 160–200.

DISCUSSION

Evans (1944) has shown clearly with chest leads that 2 : 1 A-V block often occurs in paroxysmal tachycardia, but has been overlooked.

A re-examination of older records, with standard leads only, confirms this discovery. The presence of 2 : 1 block can be found in about one-quarter of the records, but in another quarter there is good evidence against the view that it is always present. The remaining half provide no conclusive evidence, so the frequency of 2 : 1 block will have to be decided by examining further patients with chest leads.

Evans found 2 : 1 block in all of 27 consecutive cases which would suggest that it was almost, if not quite, the rule. But he included some cases of paroxysmal flutter and a proportion of his series were examples of one sub-division of paroxysmal tachycardia with serious heart disease and " terminal " paroxysms, which differs in some ways (the response to digitalis, the tendency to change to auricular fibrillation, and the frequency of 2 : 1 block) from the common type of paroxysms that often recur for years without much more significance than their inconvenience.

He also quoted the long series of cases of Barker *et al.* (1943), and of Decherd *et al.* (1943), with paroxysmal tachycardia and 2 : 1 block, but here too the authors emphasize, though from rather different points of view, that they are dealing with somewhat unusual examples of paroxysmal tachycardia.

Evans claims that the rate alone distinguishes paroxysmal tachycardia and flutter which are fundamentally the same. " Auricular flutter is paroxysmal tachycardia in which a moderate auricular rate (200–260) facilitates the finding of A-V dissociation. . . . Again, paroxysmal tachycardia is auricular flutter where the more rapid auricular rate (260–500) prejudices the recognition of the auricular waves hidden within the ventricular complexes and hinders the discovery of 2 : 1 A-V dissociation." This cannot be accepted. At rates below 130 (auricle 260, if 2 : 1 block is present), or even below 140, flutter is common and paroxysmal tachycardia is less common: with a ventricular rate above 180, paroxysmal tachycardia is common and flutter is rare. But with ventricular rates between 140–180, the percentages of each are almost the same (see Table IV) and paroxysmal tachycardia is more common only because it is a more common disorder.

It is probably true that there is no single criterion by which paroxysmal tachycardia and flutter can be distinguished. The shape of the curves denoting auricular activity is probably

the best. This shape (in leads II and III) in flutter, is often so characteristic that any student can be taught in a few minutes to recognize most cases of flutter.

It is open to question how atypical these may be and still allow the diagnosis of flutter. In the past, I (and perhaps others) have been too much influenced in such an atypical case by the presence of 2 : 1 A-V block in diagnosing flutter (see Fig. 8 and text). If there is no period on the iso-electric level and the curve rises (generally more sharply) and falls (generally less sharply) with regularity, the case should be diagnosed as flutter. If there is a period on the iso-electric level interrupted by something that may represent a normal or inverted P wave, the case should be diagnosed as paroxysmal tachycardia. No decision should be made on the presence or absence of 2 : 1 block, though this will be a more constant feature of flutter.

Evans here stressed that there are exceptions to all the points used for clinical differentiation. This is true, but it is also true of much differential diagnosis. If clinically, all or most of the points favour a diagnosis of flutter, it will generally be found that the cardiogram does also. In my opinion, the diagnosis should be made on the electrocardiogram alone and when this has been done, the following clinical points, set out in tabular form, will generally point in the same direction:

Paroxysmal tachycardia	*Paroxysmal auricular flutter*
Is found more often with a heart that is otherwise normal (at least 55 per cent).	Is rarely found except with a heart that is diseased.
Generally starts before the age of 40 (76 per cent).	Generally starts after the age of 40 (88 per cent).
The attacks are shorter: not often 4 days, rarely more than 10 days, and very rarely 30–40 days: it is not an established rhythm.	The attacks are longer; they may be of any length and are generally days rather than hours; it is more often an established than a paroxysmal rhythm.
It does not often change to auricular fibrillation (spontaneously or with digitalis), nor lead to established fibrillation—though any of these things may occur.	It readily changes to auricular fibrillation with digitalization, and paroxysms of fibrillation and flutter often occur in the same patient.
The ætiology is not like that of auricular fibrillation.	The ætiology is like that of auricular fibrillation.
2 : 1 or other degrees of A-V block are not readily induced by pressure on the carotid sinus or by digitalization.	2 : 1 or higher grades of A-V block are readily induced by pressure on the carotid sinus or by digitalization.
The usual ventricular rate is between 140 and 220 (88 per cent).	The usual ventricular rate is between 120 and 180 (83 per cent) or 120 and 170 (76 per cent).

Conclusions

Evans' demonstration of 2 : 1 A-V block in paroxysmal tachycardia has been confirmed in some cases, though not in all.

It is most easily seen and most frequently present in paroxysmal tachycardia that is relatively terminal in patients with diseased hearts, but is not confined to these cases.

The rate alone does not provide adequate grounds for distinguishing paroxysmal tachycardia and paroxysmal auricular flutter.

The clinical pictures of the two differ, but there are exceptions to each of the grounds for differential diagnosis.

The diagnosis of auricular flutter should be made on the shape of the auricular curves and the absence of an iso-electric period, regardless of whether 2 : 1 A-V block is present or absent.

The clinical diagnosis of paroxysmal tachycardia will inevitably include some cases of flutter. When cardiographic evidence is available, a distinction should be made between the following groups.

(1) Paroxysmal auricular flutter: with regular block, most often 2 : 1; but occasionally 1 : 1 or other grades.

(2) Paroxysmal auricular tachycardia with 2 : 1 A-V block.

Possibly divisible into two types (*a*) auricular rate normal (160–250), ventricular rate half normal; certainly commoner in failing hearts after digitalization (Barker and Decherd) and (*b*) auricular rate twice normal (250–500), ventricular rate normal; possibly commoner in failing hearts and terminal paroxysms (Evans).

(3) Paroxysmal auricular (or supraventricular or nodal) tachycardia without A-V block.

(4) Paroxysmal ventricular tachycardia.

Whether paroxysmal tachycardia depends on a circus movement at some part different from the circus movement of auricular flutter or not, is still unsettled.

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IMMERSION AS A FACTOR IN THE DEVELOPMENT OF HYPERTENSION

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During the course of routine physical examinations of men admitted to an Emergency Medical Service neurosis centre it was noticed that high blood pressure readings were being recorded not infrequently. The impression was formed that the high values were more frequent in men of the Merchant Navy who had been shipwrecked.

It seemed worth while to attempt to confirm the presence or absence of an abnormal degree of vasomotor reaction in such men, especially as some work has already been done to show that there is possibly just such an exaggerated vasomotor reaction in those subjects who are potential candidates for the later development of essential hypertension (Hines and Brown, 1933).

The working hypothesis formed was that, as a result of exposure to cold for abnormally prolonged periods under circumstances increasing heat loss to an unusual extent, there is a reflex vasoconstriction of renal vessels which is prolonged sufficiently to produce damage to the kidney. Moreover, such exposure may bring about changes in the kidney so that in future it is hypersensitive to cold stimuli applied externally, or that the cycle of events leading to production of pressor substances may be initiated. It was planned originally that in each case investigated an estimate of renal function would be made, but this proved to be impossible owing partly to the shortage of laboratory staff, the pressure of routine work, and the shortage of nursing staff. Only ward testing of the urine for albumen was carried out on admission. No abnormalities were found in any case.

A group of 15 physically fit men of the Merchant Navy, all of whom had been immersed, were taken, in succession, on their admission and were used for the investigation.

To act as controls a group of non-immersed neurotic men and a group of non-immersed non-neurotic men were also tested in the same manner.

The test used was practically identical with that described by Hines and Brown (1940) and will be detailed below.

The Cold Pressor Test

The tests were all carried out in a quiet room with which the men were familiar and in which they had been lying recumbent on a couch for one hour. To allay anxiety the nature of the test had previously been explained. With the subjects recumbent and comfortably relaxed, a series of blood pressure readings were taken at two-minute intervals until a steady basal level for three consecutive readings was obtained. A bowl of water and ice at a steady 4° C. was so arranged as to enable the free hand to be immersed up to the wrist without the necessity of any movement on the part of the subject. Immersion was maintained for two minutes while readings of blood pressure were taken at half-minute intervals. The hand was then withdrawn and dried while blood pressure readings were taken at half-minute intervals until the levels returned to the pre-immersion figures. A physical examination to exclude organic disease was also carried out. Special attention was paid to the past

* With a statistical note by Eliot Slater.

history of scarlet fever, nephritis, pyelitis, hypertension, rheumatic fever, or a family history suggestive of hypertension such as strokes or sudden death.

The normal response to the test of men within the ages of 20 to 40 is a systolic rise not exceeding 20 mm. and a diastolic rise not above 15 mm. returning to normal within 2 minutes (Hines and Brown, 1940). These observers state that as a result of analysis of a large number of tests an elevation above the basal level of more than 20 mm. systolic pressure and more than 15 mm. diastolic pressure indicates a hyper-reactive type of response to the stimulus. They quote a total of 1842 subjects with normal blood pressures and 1117 with essential hypertension in whom the results obtained show that the mean response in cases with essential hypertension is from 2 to 6 times greater than those obtained from the subjects with a normal blood pressure. Writing six years after their original investigations of 66 subjects with normal blood pressure they had traced all but three of their 24 originally " normal hyper-reactors ": 38 per cent of these were found to have developed essential hypertension, but of the 28 traced out of 42 originally " normal hypo-reactors " none had developed hypertension.

The rise in blood pressure following immersion of the hand in water at 4° C. is a reflex response, the afferent arc of which is apparently those fibres in peripheral nerves that convey sensations of pain and temperature. This is suggested by the results obtained in a patient with syringomyelia, aged 27, with anæsthesia to pain and temperature over the right arm. The results of the cold pressor test carried out on this man were as follows.

Right arm. 108/70; 108/64; 108/64. Immersion. 110/66, ½ minute; 110/64, 1 minute; 108/64, 2 minutes.

Maximum rise S/D=2/2.

Left arm. 120/58; 120/58; 120/58. Immersion. 125/85, ½ minute; 155/90, 1 minute; 150/80, 2 minutes; 130/70, 3 minutes.

Maximum rise S/D=35/32.

A similar finding was reported by Sullivan (Sullivan, 1941) in a case with complete transection of the spinal cord in the lumbar region. He found a normal response in the arms, but a response of only 10/0 in the legs.

Results Obtained

All cases were men of the Merchant Navy who had been shipwrecked, usually following torpedoeing or the striking of a mine. Of the 15 in this group, 14 had been shipwrecked within 5 to 15 months of the test. One man, case 41, had been shipwrecked 29 months previously and he gave a response to the test of S/D=5/5 returning to normal in 3 minutes, i.e. within normal limits, except as regards time which was prolonged by one minute. This man had been torpedoed off Iceland in 1941 and was in the water for five days hanging from the keel of an overturned lifeboat: he later had immersion foot. Case 20 was on a ship which was torpedoed in the North Atlantic in August 1942 and was in an open boat for 35 days; it was the rainy season and he was wet all the time. This man gave a result of S/D=72/44 taking 6 minutes to return to normal: on admission his blood pressure was 130/85. Case 11 was shipwrecked on two occasions in the South Atlantic each time. On the first occasion in 1942 he was immersed for 2 hours, the second for 34 hours. His blood pressure on admission was 185/130, and six weeks later was still 165/110, but he gave a basal blood pressure of 130/80 after 60 minutes rest before the cold pressor test was carried out. His response to the test was S/D=50/40 returning to basal levels in 5 minutes.

The above histories are typical of the more severely exposed men. In the whole group the least degrees of exposure to cold and wet were suffered by Cases 10 and 33.

In Case 10, who was immersed for not more than 2 hours, a response of S/D=40/30 was obtained, returning to normal in 8 minutes. Case 33 got straight into an open boat 500 miles off the coast of South America in midsummer. It was dry for five days and rained continually for two days, this constituting the only exposure to water. His response was S/D=16/28, returning to normal in 4 minutes.

The other 10 men received degrees of exposure varying considerably, but falling between the extremes of those related above.

The only 2 men out of the 15 in this group with family histories at all suggestive of hyper-

tension were Cases 29 and 41. In Case 29 the man's mother, aged 78, had had a stroke, and his father had died of heart failure; this sailor gave a response of S/D=12/26, returning to normal in 4 minutes. Case 41, whose father had had strokes and later died at the age of 68, gave a result S/D=5/5, returning to normal in 3 minutes, but as noted above this man was exceptional in that 29 months had elapsed between shipwreck and cold pressor test.

It is to be noted that 3 of these 15 men gave test results within the range of the normal as defined by Hines and Brown (1940). Of these, Case 18 had been shipwrecked twice: on the first occasion, 3 years before the test, he was in an open boat in the Arctic circle for 12 hours; the second time was 9 months prior to testing and he was in a water-filled open boat in mid-Atlantic—wearing only a singlet—for 10 hours. Case 31 had been torpedoed 8 months previously between Freetown and Takeradi, he was in the sea 6 hours and then in an open boat for 9 hours and said it was cold. Case 41 has already been described as one of the examples of severe exposure.

Control Group 1 (*Non-immersed Neurotic*). This group consisted of 9 patients with the diagnosis of anxiety state, in whom there was no evidence of any organic disease, neither had any of them ever been shipwrecked. In this group Case 25 gave a result outside normality, but he gave a past history of frequent attacks of tonsillitis. Case 27 gave an abnormal diastolic response to the test and also took 4 minutes to return to normal. Case 45 gave an abnormal diastolic response and took 3 minutes to return to normal, but here it is interesting to note that a past history of scarlet fever and nephritis were obtained and he now suffers from backache and has frequency of micturition.

Control Group 2 (*Non-immersed Non-Neurotic*). Eleven men constitute this group: all were patients in a general medical ward who were awaiting discharge home having recovered from such ailments as fibrositis, minor upper respiratory infections, and peptic ulcer. No member of this group had been shipwrecked and all were passed as normal from the psychiatric point of view. Case 51 gave an S/D rise of 13/25, returning to normal in 3 minutes. This man had spent 3 years in a Prisoner of War camp in Poland where the temperature was often 30°–40° F. below freezing. Case 38 with an S/D rise of 22/20 and a return to normal in 3 minutes was anxious and would not relax during the test; his disability was fibrositis of the back. Case 36 with an S/D rise of 18/19 returning to normal in 3 minutes, swims a great deal and took part in seaborne invasion, necessitating wading for some time and the usual pre-invasion exercises. Case 50, with a dislocated ankle, had never been immersed; he was 24 years old and gave the abnormal S/D rise of 29/32 taking 4 minutes to return to normal. Case 49 also gave a family history that his father had died at 65 years having had three strokes and his paternal aunt also died following a stroke; his S/D rise was 18/16 and took 4 minutes to return to normal. It is worth noting that case 47 with an S/D rise of 4/9 returning to normal in 2 minutes is a non-swimmer.

Statistical Results by Eliot Slater

The results of the tests are given in Table I, and their statistical analysis in Table II. No correlation was found between the test results and the bodily habitus—asthenic, athletic, or pyknic—or between test results and psychiatric diagnosis—anxiety state, hysteria, depression, etc. We may note from Table I that there are small differences between the three groups in respect of age and systolic and diastolic blood pressure, but that much bigger differences are found in the test results. The immersed men gave a mean systolic rise of 25 mm., a mean diastolic rise of 23 mm., and the rise of blood pressure was maintained for a mean time of 5 minutes. In the other two groups the corresponding figures are: (non-immersed neurotic) 13 and 15 mm. for 3·4 minutes and (non-immersed non-neurotics) 14 and 15 mm. for 3·1 minutes.

The ages of these men and their basal systolic and diastolic blood pressures, which are also recorded, do not show any significant differences between the three clinical groups. Furthermore, they do not show any significant association with the factors analysed above. They can therefore be neglected for the purpose of discriminating the immersed men from the others.

TABLE I.—RESULTS OF THE TESTS

No.	Age	Systolic pressure	Diastolic pressure	Systolic rise	Diastolic rise	Time required to return to normal as ½ minutes	Discriminant function calculated from S.R., D.R. and T.
				Immersed			
6	23	150	75	20	25	12	5·0
10	36	125	68	40	36	16	6·7
11	23	130	80	50	45	10	4·0
16	22	114	50	11	20	14	5·9
18	36	120	64	15	6	10	4·4
19	41	104	72	41	22	10	4·3
20	23	108	76	72	44	12	5·0
22	40	132	90	23	15	8	3·4
26	24	126	65	14	25	8	3·2
29	35	118	64	12	26	8	3·2
30	30	135	75	20	21	10	4·2
31	36	125	72	10	10	6	2·5
32	21	108	62	22	18	10	4·3
33	23	126	72	16	28	10	4·1
41	26	145	75	5	5	6	2·6
Mean	29·2	124·4	70·7	24·7	23·1	10·0	4·19
				Non-immersed neurotic			
7	23	125	75	10	13	6	2·5
9	24	130	60	10	8	6	2·6
23	24	122	58	3	12	5	2·0
25	36	118	75	22	15	8	3·4
27	21	120	76	20	29	8	3·2
43	37	120	78	10	8	6	2·6
44	25	128	70	12	12	6	2·5
45	24	112	65	18	25	6	2·4
46	21	120	80	15	15	9	3·8
Mean	26·1	121·7	70·8	13·3	15·2	6·7	2·78
				Non-immersed non-neurotic			
35	26	105	60	15	10	6	2·6
36	39	120	76	18	19	8	3·3
37	24	122	64	8	11	5	2·1
38	37	138	85	22	20	6	2·5
39	44	120	75	4	0	4	1·8
40	22	132	94	8	16	6	2·4
47	21	130	76	4	9	5	2·1
48	25	116	65	16	9	6	2·6
49	39	110	68	18	16	8	3·4
50	24	105	64	29	32	8	3·2
51	24	115	70	13	25	6	2·3
Mean	29·5	119·4	72·5	14·1	15·2	6·2	2·57

TABLE II.—STATISTICAL ANALYSIS OF RESULTS

	Degrees of freedom	Systolic rise in blood pressure	Diastolic rise in blood pressure	Time taken to return to the basal blood pressure	Discriminant function
Total variance	34	6590·68	3736·57	247·88	43·36
Percentage attributable to:					
(*a*) Difference between immersed and non-immersed men	1	15·69	14·20	44·81	46·16
(*b*) Difference between sub-classes of non-immersed men	1	0·04	0·00	0·47	0·49
(*c*) Variance within groups (error)	32	84·27	85·80	54·72	53·35
(*d*) Variance ratio (a/d.f. : c/d.f.)	—	5·96	5·28	26·21	27·68
Probability less than	—	0·05	0·05	0·001	0·001

Systolic rise, diastolic rise, and time are all closely related variables. They form different aspects from which the function that differentiates immersed from non-immersed men can be viewed. Using all three variables together to measure their discriminant function as accurately as possible, the correct proportions in which each should be weighted are S.R. +0·0058, D.R. −0·0147, T. +0·4390 (for procedure used see Mather, *Statistical Analysis in Biology*, p. 152, London, 1943). The variable X shown above is the weighted sum of the three measurements for each man. When analysed, as shown, it is found not to discriminate significantly between immersed and non-immersed men better than T alone. Therefore, although systolic and diastolic rises are relevant information for discriminating between the two groups, they can be neglected when time has been recorded.

Since non-immersed neurotic men do not differ from non-immersed non-neurotic men in respect of systolic rise, diastolic rise, time taken to return to basal blood pressure, or the weighted combination of all three, it is reasonable to infer that these characteristics differentiate immersed men from normal men as a consequence of immersion and not as a consequence of neurosis.

Discussion

We conclude, therefore, that there is a significant difference in the test results between the men who had been exposed to wet and cold and those who had not. This tends to support the hypothesis, from which we started, that such exposure if severe and prolonged can be expected to have a damaging effect on the normal kidney.

That there is an association between exposure to cold and/or wet and alteration in renal function is well substantiated. As early as 1873 Johnson in a paper read before the Clinical Society of London described how a medical student of 22 years, previously healthy, developed albuminuria, fatigue, and headache after a cold bathe of only fifteen minutes. The albuminuria on this occasion lasted only twenty-four hours. One week later a further cold bathe caused a repetition of the symptoms, but on this occasion the albuminuria persisted for nineteen days. Two further cases of albuminuria after bathing were described by Johnson where it was known that none existed before. Unfortunately at that time estimation of blood pressure was not easily carried out, neither were casts looked for in the urine.

Mudd and Grant (1919) showed that on chilling the skin of the back there followed a marked depression of the temperature of the pharyngeal mucous membrane in normal subjects, the fall being due to vasoconstriction and not to a fall in blood pressure or blood temperature, both of which in fact rose slightly. They found that whereas the skin readily regained its pre-cooling state as regards temperature the mucosa on the other hand showed a prolonged fall of temperature and did not regain its normal temperature in twelve minutes. This may indicate a prolonged vasoconstriction of the mucosal vessels in the pharynx. This observation of Mudd and Grant serves to indicate that the vasoconstrictor changes are not confined to the skin after exposure to cold. The albuminuria noticed by Johnson after bathing may likewise indicate a functional connection as regards response to cold or pain between the skin and renal vessels.

As regards the intensity of the stimulus that results from immersion in cold water, it must be noted that the cooling effect of water is fourteen times as great as that of air. Thus a cold bath at 4·4° C. causes the heat production of the body to increase twelve-fold in the first ten minutes. After this the heat production mechanism becomes depressed and the body temperature begins to fall (Best and Taylor).

The actual stimulus causing these changes is not the perception of the degree of coldness, but the pain associated with the lower ranges of temperature when perceived for a longer period. This mechanism of the response of the blood pressure to cold is borne out by the observations of Pickering and Kissin (1936), who thought in the small series of patients examined by them that the size of the response seemed to be related to the degree of discomfort that the subject experiences, and was to a large extent independent of the resting blood pressure. In their investigation immersion was carried out for the slightly longer period of three minutes.

Wolf and Hardy (1943) concluded that the cold pressor effect is a measure of reaction to

pain and that such pain is altogether separate from the sensation of cold itself. The pain is probably mediated through small non-myelinated fibres of class C. In the case of syringomyelia described in the first part of this paper no significant rise in blood pressure was obtained on immersing a hand devoid of pain and temperature sense, whereas the other hand with intact sensation consistently gave a hyper-reactive response. It would be interesting to know what the response in cases of hysterical anæsthesia would be.

Experimentally Ariel *et al.* (1943) found that rabbits exposed to a temperature of 3° C. for periods up to 48 hours secreted no urine during this time though the animals were incontinent of fæces (presumably the normal habit in rabbits). This may suggest a profound degree of renal vaso-constriction as a result of cold in the rabbits, together with a fall in metabolic rate generally.

Wertheimer (1894) showed experimentally that cooling of the skin caused a contraction of the renal vessels.

It is interesting to note that other factors are probably concerned in producing persistent hypertension. Thus Graham (1945) showed in a representative sample of all ranks and services of an armoured brigade of considerable experience in Western Desert campaigning that in 695 men a mean blood pressure of 154/90 was found. Of these 695, 27 per cent had diastolic pressures over 100 mm., and 38 per cent had systolic pressures over 160 mm. Two months later 28 of this 27 per cent. had returned nearly to normal as regards blood pressure. Graham is of the opinion that prolonged and repeated battle strain with its hyper-adrenalinæmia, as shown by the fast pulse, pale face, and enlarged pupils, is the chief factor responsible. In a catastrophe such as shipwreck any hyper-adrenalinæmia produced as a result of emotional reaction would serve to accentuate further the response to the cold immersion itself.

Observations by Homer Smith (1939) are also indicative of variations occurring in renal blood flow as a result of emotion. During the estimation of renal blood flow by means of diodrast clearance, inulin clearance, cardiac output, and urine flow, Smith noticed in one subject that during the third estimation " a rumour of a disturbing nature . . . reached the subject . . . the only objective signs of autonomic disturbance were marked sweating of the face and hands, but the renal blood flow was abruptly decreased by 40 per cent. Another subject during the tests misinterpreted their significance and " became increasingly restless, alarmed, and remonstrative "; during the peak of this phase the degree of renal vaso-constriction that occurred " was as profound as any we have seen after the administration of large doses of adrenalin." No mention, however, is made as to the presence or absence of albuminuria during these episodes.

The foregoing results may be interpreted as showing that following prolonged immersion in cold water an alteration in response to the test used is found between the immersed and non-immersed groups. It is conceivable that cold causes a reflex contraction of afferent or efferent arterioles of such a degree that the delicate glomerular apparatus becomes damaged and thus rendered permeable to albumen which is then excreted in the urine. At the same time the ischæmic kidney as a self-protective mechanism causes a rise in systemic blood pressure by means of its pressor substances, as an ischæmic kidney is well known to do. If the period of renal ischæmia is short then the glomerular damage may be slight and non-progressive or reversible, but if of longer duration, probably of some hours, then the changes induced may no longer be reversible and the renal tissue may become hypersensitive to further short periods of ischæmia induced by short periods of exposure, or to exposure to temperatures which would previously have been ineffectual in bringing about the response. In this way a vicious cycle may be set up which leads to the development of established hypertension.

SUMMARY

Men of the Merchant Navy, who had been shipwrecked, were noticed on admission to hospital to show a high incidence of raised blood pressure. The response of such shipwrecked men to a standard " cold pressor test " is shown to be different from that of two control groups. The results are analysed statistically and there is seen to be a significant

difference between the three groups: analysis shows this difference to be associated with the factor of immersion. The possible significance of this difference is discussed in its relation to hypertension.

I wish to express my appreciation to Dr. Denis Hill for much helpful criticism during the investigations and also to Dr. Terence East for helpful suggestions and criticisms.

The investigations were carried out at Sutton Emergency Hospital, Sutton, Surrey.

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WILLIAM RITCHIE

The name of William Ritchie, who died on February 7, 1945, will always be associated with the recognition of Auricular Flutter: forty years ago, on June 23, 1905, he recorded clear auricular waves at a rate of 274 to the minute in a venous tracing from the jugular vein of a case of heart block. Thereafter in many papers he established its clinical and instrumental recognition, and suggested the name of auricular flutter.

Born in Edinburgh on November 5, 1873, Ritchie received his early education at Edinburgh Academy, and graduated in medicine in 1896 as M.B., C.M. of the University of Edinburgh. At school and at the university he was a contemporary of Edwin Bramwell, whose sympathetic memoir in the *Edinburgh Medical Journal* recalls the chief incidents in Ritchie's life. They both graduated on the same day, and enjoyed a lifelong friendship. From his student days it was, apparently, recognized that Ritchie had the capabilities for making a name for himself in medicine. He was also a keen football player, and for many years played forward for the Edinburgh Academicals.

After qualification he was house physician to Dr. Affleck at the Royal Infirmary, Edinburgh, and afterwards served as house surgeon to Mr. Pringle in Glasgow. Following these house appointments, he went to Vienna for some months, learned German, and came under the influence of Wenckebach. On his return to Edinburgh he did some bacteriological research in the laboratory of the Royal College of Physicians, and in 1900 published a paper on the bacteriology of bronchitis. From 1900 to 1905 he worked in Dr. George A. Gibson's wards as Clinical Tutor. There is no doubt that Gibson's influence and the opportunities in his wards stimulated Ritchie's interest in cardiovascular diseases. It was through Gibson's influence that a laboratory for clinical research was instituted in the Royal Infirmary. Ritchie's entry into medicine coincided with the enthusiastic adoption of Mackenzie's methods of graphic representation of irregularities of the heart beat, and Ritchie was one of Mackenzie's first disciples. He was also one of the first to work with Einthoven's string galvonometer.

Ritchie took the Membership of the Royal College of Physicians, Edinburgh, in 1900, and was elected a Fellow in 1903. In 1905, in recognition of his work on cardiovascular disease, he was elected a Fellow of the Royal Society of Edinburgh. At this time he was gaining considerable experience in the post-mortem room as pathologist to the Leith Hospital from 1902 to 1906, and from 1906 to 1910 he was Assistant Pathologist at the Royal Infirmary. In 1911 he was appointed Assistant Physician to the Royal Infirmary. During these years he published papers on heart block, both on his own account and with Dr. George Gibson, and together they published a historical instance of the Stokes-Adams syndrome in 1909. In 1911 Jolly and Ritchie published a very comprehensive account of auricular flutter and fibrillation in *Heart* (Vol. II, 1910–11). It was Ritchie who gave the name of auricular flutter to the rapid co-ordinate contractions of the auricles. He was well aware that MacWilliam had produced similar rapid co-ordinate contractions by faradizing the auricles in cats and dogs which he described as a rapid flutter (1887). Ritchie and the writer of this memoir spent three days with MacWilliam in 1909 when he showed us his methods of producing both flutter and fibrillation. MacWilliam at this time was also interested in the subject of blood pressure, and he had a large artificial schema of the circulation in his laboratory. In 1913 Ritchie became Physician to the Deaconess Hospital, and in 1914 published his book on *Auricular Flutter*, and included a record of all the then-known cases.

In the spring of 1914 Ritchie and the writer spent ten days in Düsseldorf, Cologne, and Bonn. Two non-medical episodes stand out in my mind; we stood in the middle of the Hohenzollern Bridge in Cologne and looked at the new Hindenburg Bridge rather higher up the river, which was not yet opened, and speculated that the reason of its building was for the conveyance of troops. We spent another day with Professor Verworn, the physiologist at Bonn University, and as we passed through the rooms of his private house we kept picking up and admiring military dolls from the various chairs and settees, and Verworn remarked that

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the whole country was talking about war. He told us, also, that he spent part of his summer vacation with his family at an English watering place, and on leaving him we suggested that at his next visit he might be inclined to visit our medical schools.

When war came in August 1914 Ritchie was called up on the staff at the 2nd Scottish Hospital as Captain R.A.M.C.(T.), but being determined to see active service he joined the 1/3rd Scottish Horse and found himself with his squadron in the Newcastle area, and during his sojourn in this district he spent much time in the Newcastle Infirmary. He went with the Scottish Horse to Gallipoli, and wrote many interesting letters of his experiences on the Peninsula. Later he was in charge of the Medical Division of the 27th General Hospital in Egypt, where he remained to the end of the war. He was mentioned in despatches and awarded the O.B.E., and in 1920 he published (jointly) a review of heart cases in the E.E.F. (1916–1918). While in Egypt he met his future wife, whom he married shortly after the war.

In 1919 Ritchie returned to Edinburgh and resumed his hospital work and consulting practice in Edinburgh, and in 1922 he was appointed full Physician to the Royal Infirmary, and became Principal Medical Officer of the Edinburgh Insurance Company.

As adviser to the Ministry of Pensions he organized the post-war disposal of V.D.H. and D.A.H. cases in the east of Scotland. Similar advisers in regions of England and the west of Scotland used to meet twice a year at the Ministry of Pensions for some years after the war, and it was this company of friends, interested in the same sort of work, who decided in 1922 to start the Cardiac Club when the meetings under the auspices of the Ministry of Pensions ceased. Ritchie was one of the keenest members, and acted as Treasurer from its commencement to 1931.

In 1928 Ritchie succeeded Professor Gulland as Professor of Medicine, and reorganized the systematic teaching of medicine, retiring from the University Chair in 1937. He held office as President of the Royal College of Physicians from 1935 to 1937, and in 1923 and 1935 he collaborated with his friend John Cowan in the 2nd and 3rd editions of Cowan's book *Diseases of the Heart*. Throughout his professional life he maintained constant touch and friendship with John Cowan of Glasgow. Ritchie gave the Gibson Memorial Lecture in 1922 on " The Response of the Heart in Health and Disease," and in 1939 the St. Cyres Lecture, taking as his subject " Rheumatic Heart Disease."

At the outset of this war Ritchie took over temporary charge of the wards of an absent colleague at the Royal Infirmary, and was made Physician to the Emergency Medical Hospital at Bangour, so that he continued his ward teaching to the end of his days.

A year before he died the University of Edinburgh conferred upon him the honorary degree of LL.D.

Ritchie gave to Edinburgh the knowledge of the cardiovascular system which the work of G. A. Gibson, Mackenzie, Lewis, and Wenckebach had made possible, and to this knowledge Ritchie made valuable additions. From 1905 to 1913 he published at least twenty contributions on cardiovascular disease, and they all included his own personal work and observations. Far into the night he puzzled over and analysed polygraph tracings and electrocardiograms. The mechanism of the heart beat was being elucidated by many workers, and the early collection of records of heart block, auricular flutter and fibrillation, paroxysmal tachycardia, and the extrasystole was a fascinating pursuit. All Ritchie's work in these fields was characterized by scrupulous care.

As a ward teacher and an academic lecturer Ritchie never lost sight of the essential facts of clinical medicine and his knowledge was not confined only to disorders of the cardiovascular system. As an examiner he was somewhat frightening, but again scrupulously fair.

He was a somewhat shy person and never played to the gallery, and, as Edwin Bramwell has said, " his best qualities were not on the surface." His austerity was only equalled by his sincerity. His Promoter's address to the graduates at the Graduation Ceremonial on July 22, 1936, set forth his " Philosophy of a Doctor." It ended with these words, " May the story ultimately to be told of each of you be one that is abiding everywhere without visible symbol, woven into the stuff of other men's lives." Ritchie's high principles and conscientious work must have been woven into the lives of many generations of Edinburgh students.

W. E. HUME.

PROCEEDINGS OF THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

The NINTH ANNUAL GENERAL MEETING of the Cardiac Society of Great Britain and Ireland was held at The Royal Society of Medicine, London, on Thursday, April 12, 1945, under the Chairmanship of DONALD HALL.

The Chairman took the chair at 10.0 a.m.; 41 members and 22 temporary members and visitors were present.

The Chairman spoke of the loss that the Society and British Medicine had sustained in the death of Sir Thomas Lewis, F.R.S., who had accepted the Chairmanship for this meeting, and also by the death of W. T. Ritchie, the first Treasurer of the Society (1922–1931). He also welcomed the Canadian and American visitors.

An obituary notice of William Ritchie is on page 207: *one of Sir Thomas Lewis will be in the January number.*

PRIVATE BUSINESS

1. The minutes of the last meeting having been printed in the Journal (6, 247, 1944) were approved and signed.
2. The accounts, audited by East and Parsons-Smith, were approved: they showed a balance of £40 7*s*. 5*d*. The Council had decided that no subscription should be collected for the year 1945–46.
3. The Secretary, on the recommendation of the Council, was reappointed for another year, and William Evans was again asked to act as Assistant Secretary.
4. Three Ordinary Members were elected as *Extra-Ordinary Members*.

G. A. Allan	Sir Maurice Cassidy	A. M. Kennedy

5. The following new members were elected:—

Ordinary Members	*Associate Members*
R. Hilton	R. J. Duthie
F. G. Hobson	F. M. Hilliard
T. Skene Keith	J. G. M. Hamilton
Bruce Maclean	E. Graham Jones
B. E. Schlesinger	W. R. Snodgrass

Nine Associate Members were re-elected for another period of three years.

6. J. W. Brown, Grimsby, and H. Wallace-Jones, Liverpool, were elected members of the Council for the years 1945–49.
7. The Secretary reported that:
   (1) He had received a letter from the Association of Physicians asking the Cardiac Society to consider the relationship between the Association and the various specialists' clubs and societies and that, with the approval of the Council, he had replied " that the general policy of the Cardiac Society had been to meet in the same town on the day before the Association and that they had no intention of changing this policy, though they wished to be free to make other arrangements from time to time, and that they would welcome a suggestion that at some meetings a session should be set aside as a joint meeting of the Association and the Cardiac Society and felt that this would be to the advantage of both bodies: at the same time the Council did not think it would be desirable for the Society to lose its identity or become a branch of a larger or wider Association."
   (2) The Council had considered the question of Empire members and had decided to hold a special meeting to take further decisions in this matter. They wished the general approval of the Society for such a step and suggested that at the next Annual General Meeting they should bring forward detailed proposals of how this could best be carried out and any necessary changes in the rules of the Society. They thought that the question of a larger number of ordinary and associate members, with any necessary changes in the rules, should be considered at the same time. The Society gave general approval to some such development.

Short Communications

Auricular and Pericardial Pressures and Cardiac Output in a case of Malignant Pericarditis

C. M. Fletcher (*introduced*)

(Published in full 1945, 7, 143)

The Carotid Shudder

David Lewes (*introduced*)

(Published in full 1945, 7, 171)

Electrocardiograms of a Dying Heart a few hours after the onset of Coronary Thrombosis

T. F. Cotton

Experimental Auricular Fibrillation

A. Morgan Jones and W. Schlapp (*introduced*)

The authors described experiments with the cat heart-lung preparation in which auricular fibrillation was induced and the cardiodynamics of the arrhythmia studied. A method of measuring the work capacity of the heart (cardiac reserve) was described and it was found that fibrillation reduces the cardiac reserve of the denervated cat heart by about one-third.

When fibrillation is induced at work rates which can be maintained during the arrhythmia, the heart output falls abruptly but is gradually restored to the original amount; the restoration of output is accompanied by a rise of auricular pressure. This period was termed *adaptation.* A period of *stabilized fibrillation* follows; during this the mean heart output and auricular pressure remain unchanged. When normal rhythm is restored the heart output rises above the original amount, the excess output quantitatively making up for the deficit acquired during the adaptive period. This period was termed *recovery.*

If the normal rhythm work rate at the onset of the arrhythmia exceeds the maximum work of which the heart is capable during fibrillation, the heart output is not maintained during fibrillation and the rate of work falls to the maximum fibrillating work rate. In these circumstances no stable state is achieved, for the auricular pressure continues to rise, the heart dilates beyond its optimal size and heart failure ensues. This outcome can be avoided only by reducing the work of the heart.

Cardiac Enlargement with Bradycardia in Recruits

Crighton Bramwell

This communication concerned 39 cases that had been referred by medical boards of the Ministry of Labour and National Service on account of suspected cardiac enlargement for which there was no obvious cause. In 26 of these X-ray screening failed to confirm the presence of enlargement. Of the remaining 13, enlargement in 7 was trivial, and 4 of these were men of powerful physique, in whom slight enlargement was not unexpected. In 3 cases pathological cause for the enlargement was found, but the remaining 3 were healthy athletes, one a cross-country runner aged 34, the other two young men, aged 19 and 20, who participated actively in games and in both of whom the sitting pulse rate was 50.

The occurrence of cardiac enlargement in athletes who indulge in those forms of sport which necessitate prolonged and severe physical exertion is well known, but to what extent this enlargement is due to their training and to what extent it may be a congenital peculiarity it is not possible to say.

Comparative physiology shows that the heart ratio is high in athletic animals and low in sedentary animals, and there appears to be a general law that those animals which have a high heart ratio tend to have slow pulses with considerable vagal inhibition, while animals with a low heart ratio have rapid pulses over which the vagus exerts little influence. It is suggested that young healthy men with large hearts and slow pulses may be comparable to animals with a high heart ratio.

Two Cases of Malignant Hypertension Treated by Nephrectomy

C. Bruce Perry

(Published in full, 1945, 7, 139)

2 : 1 Heart Block in Paroxysmal Tachycardia

Maurice Campbell

(Published in full, 1945, 7, 183)

Heart Failure in Generalized Paget's Disease

O. G. Edholm (*introduced*), S. Howarth (*introduced*) and J. McMichael

A case of Paget's disease with œdema and venous congestion was found to have a cardiac output of over 13 litres a minute. By plethysmography it was shown that the blood flow through the affected humerus was increased to about 20 times the flow through a normal bone. With extensive skeletal involvement the skeletal blood flow may be increased from a normal value of the order of 100 c.c. a minute to 3–4 litres a minute. This is responsible for the resulting hyperkinetic state of the circulation, with a collapsing pulse and manifestations of " cardiac failure." (*Clin. Sci.*, 1944, **5**, in press).

The Effect of Nitrite on the Inverted T Wave

Wilfred Stokes (*introduced*)

(To be published in full)

Discussion on Patent Ductus Arteriosus and its Surgical Treatment

The contributions of A. R. Gilchrist (1945, 7, 1), Geoffry Bourne (1945, 7, 91) and Terence East (1945, 7, 95) have been published in full.

John Hunter (*introduced*) spoke of the surgical methods he had used in ligaturing the patent ductus and of some of the difficulties. He emphasized the striking nature of the thrill felt even when it was not obvious on ordinary clinical examination.

J. W. Brown said his experience showed that the outlook in patent ductus arteriosus was not altogether unsatisfactory without surgery. His remarks were based on 63 cases of patent ductus with a " machinery " murmur ranging in age from 3 to 45 years. There were 20 males and 43 females, and the periods of observation were for 16 cases, 5 years or less; 18 cases, 6–10 years; 29 cases, 11 or more years. Fourteen cases were below the average in development. The electrocardiogram showed a normal axis in 46; left axis in 9; and a right axis in 1. Two cases have died of bacterial endocarditis at the ages of 12 and 15. Regression of physical signs occurred in 2 cases. A slide was also shown of patent ductus in identical twins where the shunts were of different sizes, the larger shunt being accompanied by underweight and stature in comparison with the smaller shunt. It was felt that there may be some indication for surgery in cases that are undersized, and who fail to develop normally, but undoubtedly many cases tolerated their lesion well, and in the above series there had been 8 pregnancies and no example of congestive failure.

Disease of the Pericardium

Terence East opened the discussion.

In dry pericarditis the friction sounds are diagnostic, but sometimes the diagnosis from adjacent pleural friction is very difficult. It is curious how extensive pericarditis may be found at autopsy without friction sounds being audible during life. The cause of dry pericarditis is sometimes quite obscure. Such is the terminal pericarditis of renal disease, which carries such a bad prognosis. Instances of obscure origin, which clear up satisfactorily, are sometimes met with in adults. Some of these seem to develop a constricted sac later on. In children the pericarditis of acute rheumatism is part of a severe carditis. The enlargement of the heart which is usually present to considerable degree may simulate an effusion, but a large accumulation of fluid in these cases is not commonly seen. The signs of consolidation at the bases of the lungs, primarily and principally on the left side as a rule, are interesting.

There is no doubt that a rheumatic pneumonia is a cause in some cases, but in others a massive collapse also plays a part. This may be seen in adults. It is shown by the obvious restriction of expansion of the lower ribs, and the inhibition of the descent of the diaphragm on inspiration; serious embarrassment in breathing may result. It is therefore advisable to nurse these cases sitting up, instead of making them lie flat. The disappearance of much of the signs when the patient is propped up indicates the part collapse plays in causing the changes at the base of the left lung. When an effusion of any size is present in the sac it compresses the left lower lobe and causes collapse. In these circumstances it may be difficult to decide how large the pericardial effusion may be. It is probable that the sac must contain about 500 c.c. before definite signs are given. An effusion stretches the sac, and if it forms gradually a large volume can be accommodated without hindering the entry of blood into the heart. Rapid accumulation, as in hæmopericardium from rupture of the heart or aorta, causes acute tamponade, and at autopsy the heart is found to be contracted and empty. A very large effusion will also cause tamponade.

The same results are very gradually achieved in Pick's syndrome from a constricted sac. The obstruction to the inflow leads to a rise in venous pressure and consequent engorgement of the jugular veins and liver. At the same time the rate of the heart rises, the output falls and the blood pressure sinks. The pulse may be paradoxical. Pressure on the lungs causes dyspnœa. Cyanosis is common. These signs are usually an indication for paracentesis of the sac, which may be a useful and even a life-saving procedure. The site of election depends on the size of the effusion, and perhaps on its distribution, for sometimes it is loculated. The diagnosis may be helped by X-ray examination, particularly by screening, if this can be done. The diminished pulsation and slight change in shape on deep inspiration is typical, as well as the globular contour, obscuring the usual curves. The skiagram of a much dilated heart may give a very similar outline. In a simple serous effusion the cardiogram shows no characteristic changes. These depend on the underlying myocardium and are conspicuous in pyo-pericardium; concordant elevation of the R–T phase, followed by negative T waves later, appears in all limb leads, and are most conspicuous in lead II. R waves are not seen.

The diagnosis of the shrunken sac, of chronic constrictive pericarditis, is now readily made, and its relief can provide one of the most dramatic effects in surgery. But there is a fairly high proportion of failures, perhaps about 50 per cent. Examination of the sac in some cases shows that it is so thick and hard that relief is hopeless. The shadow of a calcified ring well inside the heart shadow may indicate the thickness of the sac. More information is needed on the failures. How far may isolated bands cause trouble? To what extent does removal of the front of the sac bring relief?

Although it is generally held that the heart is small in constrictive pericarditis, quite a proportion of patients have large heart shadows, perhaps about half. The low voltage curve and flat T waves are fairly constant. As to the cause of the condition, little is known. Tuberculosis may be responsible for some, probably less than was thought at first. Most seem to be completely obscure. Tuberculous pericarditis usually carries a bad prognosis. The disease reaches the sac from the mediastinal glands. Sometimes large effusions develop and need paracentesis. Sometimes the effusion is hæmorrhagic and resembles that found with malignant disease inside the sac. It may be worth while to introduce air when the effusion is large, in the hope of preventing recurrent accumulation or organization of œdema. This may occur in any case and occasionally a constricted sac results; the wall is usually very thick.

Exo-pericardial adhesions are difficult to diagnose. An obliterated sac, unless it is constricted certainly gives no signs. A large right ventricle thrusting forwards may cause a typical retraction of the left lower ribs behind. There is a good deal of doubt how much these adhesions around the sac really matter. It seems very likely that the enlargement of the heart formerly ascribed to them is really due to the accompanying valvular lesions. Sometimes there is a drag on the costal cartilages in the front of the chest, and this may cause discomfort, which resection may relieve.

C. BRUCE PERRY discussed rheumatic disease of the pericardium.

Pericarditis in acute rheumatism is essentially merely part of a pancarditis and it is therefore difficult and, I think, undesirable to consider it alone as a separate entity. Although the recognition of pericarditis in a case of acute rheumatism may have certain diagnostic and prognostic value, it has this value by its implication rather than on account of the pericarditis itself.

As far as the pathology goes the condition is essentially an acute inflammation of the

pericardium with a sero-fibrinous exudate. In severe cases there may be a great deal of hæmorrhage. Histologically it is possible to recognize the essential features of the rheumatic lesion: the same sort of cells are seen as in the classical "Aschoff" nodule but are loosely packed together as opposed to the more or less compact nodule found in the myocardium. There is always a little increase of pericardial fluid but for practical purposes this never exceeds an ounce or two.

Clinically the picture presented by a child with rheumatic pericarditis is so characteristic that it can be recognized almost at a glance. The ashen-grey cyanotic pallor, the restlessness, and the restrained short dry cough need no description. However, there is little reason to attribute these symptoms to the pericarditis: rather they should be regarded as due to the severe pancarditis—especially the myocardial lesion—which nearly always accompanies pericarditis. And the same picture is seen with no clinical evidence of extensive pericarditis.

The actual physical signs are, of course, the typical friction rub but this may be very evanescent in rheumatic cases. Cases with pericarditis usually have a great increase in the area of cardiac dullness and the cardiac shadow radiologically. However this increase in size is in the vast majority of cases due to dilatation of the heart due to the associated myocarditis. Pericardial effusion of clinical importance practically never occurs in acute rheumatism. Carey Coombs said that he had never seen a case that needed paracentesis. From my much smaller experience I can only confirm this. I have seen cases in which a paracentesis was mistakenly attempted but in these blood was withdrawn through the needle and it was, I think, clear that a dilated heart had been aspirated and not the pericardium.

It is commonly taught that the development of pericarditis in a case of acute rheumatism is a late or even terminal event and has therefore an extremely grave prognostic significance. In the vast majority of cases this is true, but not always. This is shown by the case of a little girl, aged 5 years 8 months, who was admitted to hospital with acute otitis media. Some days later she developed pain in the right hip followed in two or three days by pain in the other hip and the left shoulder. The next day there was a loud pericardial friction not all over the præcordium. An electrocardiogram showed a typical picture (Fig. 1). She rapidly

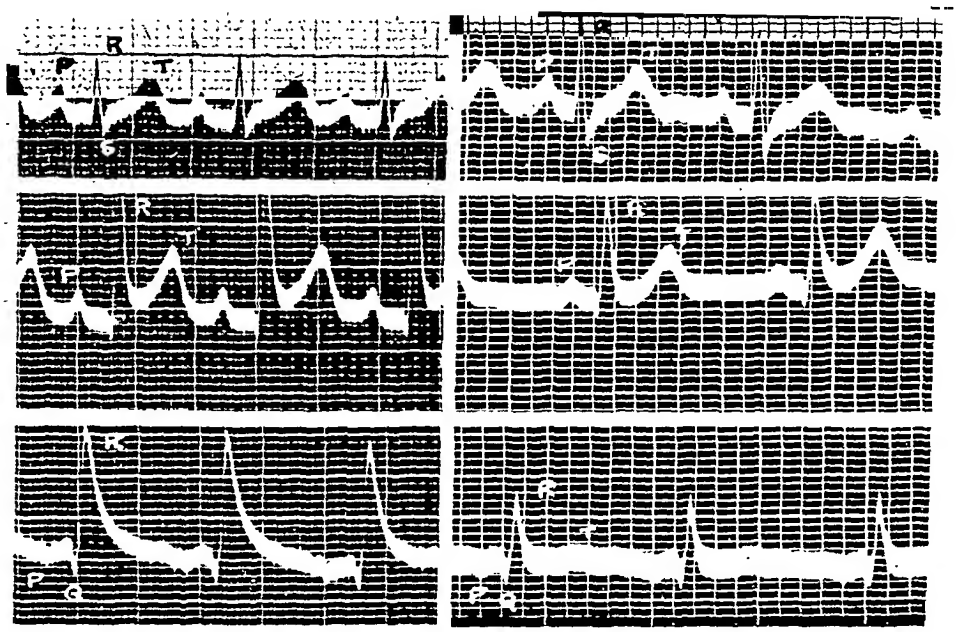

FIG. 1.—Electrocardiogram from child with rheumatic pericarditis.

improved and when the rub had disappeared there was heard an apical systolic murmur. However, with prolonged rest she finally made a complete recovery and now there is no clinical abnormality in the heart. Thus, just as in many cases the brunt of the damage falls on the mitral valve, occasionally the pericardium may be most affected.

As for treatment this must be directed to the carditis and, of course, complete and absolute rest with skilled nursing is essential. I do not use salicylates in cases with severe carditis as I have seen no evidence that they affect the course and I feel that the possible development of salicylism and vomiting would be fraught with such great danger that it is better avoided.

One drug, and as far as I know one drug alone, may be life saving and that is morphia. It should be given in doses adequate to keep the child quiet and repeated as often and for as long as necessary.

The end result of rheumatic pericarditis is, of course, pericardial adhesions and in severe cases there may be a complete fusion of the two layers of pericardium. However, it appears to be very rare for acute rheumatism to produce the picture of constrictive pericarditis. In addition to the fusion of the pericardium there may be adhesions between the pericardium and the surrounding mediastinum. It is probable that these mediastino-pericardial adhesions are responsible for the physical signs—Broadbent's sign and the peri-apical retraction. In such cases the clinical picture is usually dominated by the valvular and myocardial damage and, as in the acute phase, the pericardial lesion is a relatively unimportant component of the whole picture—the pancarditis.

JOHN PARKINSON showed lantern slides and outlined the radiology of pericardial disease, first making reference to the para-apical triangle, cysts and sacculations of pericardial fluid, and tumours. In pericardial effusion the shortened vascular pedicle is significant; the cardio-hepatic angle is preserved and not obliterated as used to be taught. A table was shown to facilitate the differential diagnosis of effusion from gross cardiac enlargement. Effusion occasionally complicates cardiac infarction, and it appears to be not uncommon in myxœdema.

In constrictive pericarditis there is neither great cardiac enlargement nor any characteristic outline. Fixation may be shown by the heart failing to fall during inspiration. Calcification is a most valuable sign present in 25–50 per cent; it is to be distinguished from calcified wall thrombi and from calcified deposits in the myocardial wall especially in cardiac aneurysm.

TUDOR EDWARDS (*introduced*) said that it was difficult to diagnose pericardial suppuration which had formed as a complication of pulmonary or pleural suppuration. In such cases the cardiac outline was obscured by a loss of translucency either in one or both lung fields. Pericardial friction might be present, but the more certain diagnosis rested with exploratory aspiration of the pericardial sac. In this event it was important not to soil the pleura and it was best to direct the needle upwards and backwards at the left xiphisterno-costal angle.

Tudor Edwards spoke at greater length about constrictive pericarditis. He said that when calcification was present it was distributed irregularly as plaques of variable size and situated between the two pericardial layers although infiltrating the heart muscle itself. It was common experience to find pockets of thick creamy material in relation to the calcified plaques, material which had always proved sterile on culture. The condition appeared to be due to tuberculosis and three out of his series of eighteen patients had died of this subsequent to the operation. It was the aim of the operation to remove a sufficient amount of the constricting scar tissue to allow free movement of the ventricles. Unless an adequate window was made through the entire thickness of the pericardium the result of the operation would be a disappointing one. In most cases the pericardium still shows the original layers and the removal of the outer layer does not effect cardiac release, and it was necessary to remove the deeper visceral layer and permit herniation of the heart over the whole area of the operative field. It was his practice to clear the front of both ventricles, and the lateral wall of the left ventricle as far as the left phrenic nerve, and to free the cardiac apex. When possible the auriculo-ventricular groove is also cleared, but the auricles and caval areas are left undisturbed for they present the greatest operative hazards and their clearance adds nothing to the value of the operation. The pericardium is removed over the left ventricle before the right ventricle, and cardiac irregularity during manipulation and dissection of the calcium plaques is lessened by bathing the exposed heart with novocain. The left pleura is frequently opened when stripping it off the pericardium but this is no great disadvantage. Improvement from the operation has not been invariable; in some it has been dramatic although seldom immediate, and it has been best in those cases where the condition has not been long-standing.

WILLIAM EVANS spoke on the electrocardiogram of pericardial disease. He said that much had been written about this, its similarity to the tracing in cardiac infarction and the ways it differed from it. Early on it had been shown that the cardiographic changes arise from injury to the myocardium and occur independently of variations in the pressure within the pericardial sac, and the foremost worker in this field was a member of the Society, Fitzgerald Peel of Glasgow.

Changes in the cardiogram of *acute pericarditis* are confined to the R–T segment in the

early stages. Like that of cardiac infarction they are short-lived and are soon followed by inversion of the T wave, but unlike that of cardiac infarction the R–T deviation differs in its direction and in its form. Thus, the reciprocal relationship of the changes in leads I and III in infarction, namely, elevation of the R–T segment in one lead and depression in another, is absent in pericarditis; in the former the curve is said to be discordant and in the latter, concordant. Again, the elevated R–T curve of cardiac infarction has its convexity upwards and shows a coving effect, while in pericarditis the curve is saddle-like because the concavity is directed upwards. While the duration of the R–T changes is no longer than a few days, the deformity of the T wave which follows will last or disappear according to the progress of the myocardial injury, and it does not depend on the presence or absence of pericardial fluid. Thus a cardiogram in acute pericarditis might return to its normal state when the effusion disappears; sometimes the tracing hardly departs from the normal in the presence of a large pericardial effusion, while gross changes may take place in the absence of effusion.

Changes in the cardiogram of *constrictive pericarditis* are most prominent in the T wave although they are not confined to this. Their location in particular leads depends on the distribution of the myocardial injury from the pericardial disease, and on the degree of right heart preponderance. The changes are permanent and are not modified materially by operation. The voltage of the tracing is low in about one-half the cases, but by itself is not of great use in the differential diagnosis. Auricular fibrillation is not uncommon even in subjects under 30. Right axis deviation is often present. The P wave is usually broad and especially in lead II, and its ascending limb commonly exhibits a step or shelf. The Q wave, very often absent in all leads, is never prominent. R–T depression or elevation are uncommon features. The T wave changes are conveniently considered in two groups. In the first type there is inversion of T III and T II, and of T in CR_1 and IVR, but not in CR_7. Some of such changes may be attributed to right heart preponderance. In the second type there is inversion of T I and T II, and of T in IVR and CR_7, while the T is low or inverted in CR_1. Naturally a few cases show a combination of changes, but the cardiographic diagnosis of cardiac infarction and constrictive pericarditis can usually be told from an examination of the above characteristics. It is unsafe to rely on the concordant or discordant T wave in differential diagnosis because a concordant T might result from infarction of the anterior and posterior parts of the heart and simulate the findings in cardiac infarction complicated by pericarditis.

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